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Original Articles

ELECTROKINETIC PHENOMENA*

XIV. THE INACTIVATION OF RAGWEED POLLEN EXTRACTS BY ADSORPTION AND THE ELECTRIC CHARGE OF THE RESULTANT SURFACE

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IT HAS been noted by numerous experimenters that filtration of ragweed extracts for purposes of sterilization results in loss of activity by the occurrence of adsorption of the active material on the surface of the filter.[1] Moreover, the active substances were also readily adsorbed by kaolin, charcoal, and other adsorbents. These results indicated that the active principle contained in ragweed extract behaves very much like serum albumin, egg albumen, gelatin, and other proteins, which are also easily adsorbed by quartz, kaolin, charcoal, asbestos, and other surfaces.[2, 3] When quartz powder or charcoal adsorbs protein, the protein imparts to the surface of the adsorbent its own electrical properties. If these protein-coated particles are made to migrate in the electric field by applying a direct current, they move with a velocity, at a given pH, characteristic of the protein.

In the series of experiments to be reported here, quartz particles (which inactivate dilute ragweed pollen extracts), as well as other types of surfaces, were added directly to ragweed extracts. The electrical properties of the adsorbed films on these treated particles were then investigated by the microscopic method of electrophoresis,[4, 5] in an attempt to determine the nature of the adsorbed active material.

The following experiment reveals how quartz particles inactivate ragweed pollen extracts. To various dilutions of the extract were added constant quantities of a fairly heavy quartz suspension. After the extract had stood for several hours to insure complete adsorption, the quartz was centrifuged, and the supernatant liquid withdrawn

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for testing. Fig. 1 indicates the type of result obtained with scratch tests on a patient sensitive to ragweed. We are indebted to Drs. R. A. Cooke and Arthur Stull for confirming the fact that quartz particles inactivate ragweed extracts. The work of numerous investigators, especially that of Cooke, Stull, and their co-workers, has indicated that the active principle is albuminous in nature.[6] It seemed, therefore, pertinent to determine if the active principles in ragweed extract could be studied by this electrical method which has been quite successful in the investigation of other substances of high molecular weight.

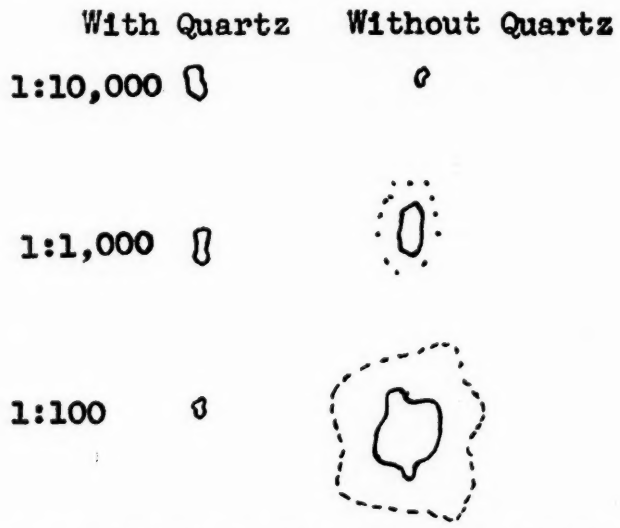

Fig. 1.—To various dilutions of ragweed extract were added constant quantities of a quartz suspension. After standing an hour to insure complete adsorption, the quartz was centrifuged and the supernatant liquid withdrawn for testing.

METHODS

Ragweed Extracts.—The ragweed employed was purchased from a commercial firm. Only extracts of giant ragweed pollen *(Ambrosia trifida)* were studied. The dried ragweed pollen was extracted in a Soxhlet apparatus with petroleum ether for several hours. The extracted ragweed pollen was then treated by means of distilled water (about 50 c.c. for each 10 grams of pollen), or else the soluble material was obtained by suspending the pollen in M/10 sodium acetate solution for several hours. Before using the aqueous extracts, the solutions were placed in Visking sacs and dialyzed against distilled water at least fifteen hours in the icebox. The ragweed pollen extracted with sodium acetate, however, could not be dialyzed in this way. In this latter instance no dialysis was employed and the crude extract was used directly. It might be of interest to make subsequent studies of this extract when dialyzed against sodium acetate, but this

has not yet been done. In any event the adsorption of the undialyzed and dialyzed material was not markedly different.

Method of Preparation of Particles.—Finely ground quartz was repeatedly sedimented to remove all but the smallest particles. These were treated with warm bichromate cleaning fluid, washed thoroughly with water, and then boiled in concentrated hydrochloric acid. After a thorough washing by centrifugation, the resultant product remained as a milky suspension for some time without settling. Although quantitative measurements are not available, the particle radii were of the order of 0.5 μ. In any case, there was no observable difference in electric mobility between large and small particles in this range when coated with the adsorbable component of the pollen extract.

The mineral oil employed was of ordinary commercial grade. Suspensions were prepared by vigorous shaking with water in a separatory funnel for about ten minutes, after which a suitable volume was withdrawn for use in the measurements. The diameter of the mineral oil droplets was of the order of 5 microns. Collodion particles were prepared by a modification of the method described by Loeb.[7] A constant number of each type of particle was used in these experiments, the suspensions being only faintly turbid.

Measurements of Electrophoresis.—The electric mobilities of the particles of quartz, paraffin oil, or collodion were determined by the direct microscopic method.[4] The particles were suspended in a glass cell of uniform rectangular cross section and observed under the microscope when a direct electric field was applied. Measurements of pH were made with the quinhydrone electrode, taking the pH of M/10 hydrochloric acid as 1.08. The reference electrode was checked against this solution or against standard acetate buffer (pH 4.70). Mobilities were corrected to 25° C. by applying a temperature coefficient of 2 per cent per degree. The room temperature was in the neighborhood of 28° C.

Nitrogen Determinations.—The determination of total nitrogen was accomplished by the Koch-McMeekin micromethod.[8]

Titration Curves.—The titration curves were determined by adding small quantities of acid or base to a relatively large volume of dialyzed extract. Inasmuch as the pH of the pure solution before addition of acid or base did not usually coincide with the pH of its isoelectric point,[9] the isoelectric point of quartz particles in some of the solution to be titrated was determined. The amount of acid or base apparently bound at the isoelectric point was then added or subtracted from each point, so that the titration curve ran through the isoelectric point. This always necessitated a slight shift in the curve. The pH of concentrated solutions of protein deviated a few tenths of a pH from the isoelectric point determined by electrophoresis.

Preparation of Suspensions.—Particles in these experiments were added to the final volume of the solution of nitrogen-containing material. An interval of fifteen minutes was allowed to elapse to make certain of relatively complete adsorption. In the experiments in which the mobilities were determined at different pH values, ten times the concentration of extract needed to insure complete coating of the quartz particles was used. This margin was quite sufficient to cover any loss of protein by precipitation from denaturation on standing.

EXPERIMENTAL

(a) *Effect of Varying Adsorbing Surfaces.*—In view of the fact that crude extracts were employed to obtain adsorption films on microscopic particles, it was necessary to determine if the constituents adsorbed would be taken out by the adsorbing surfaces independently

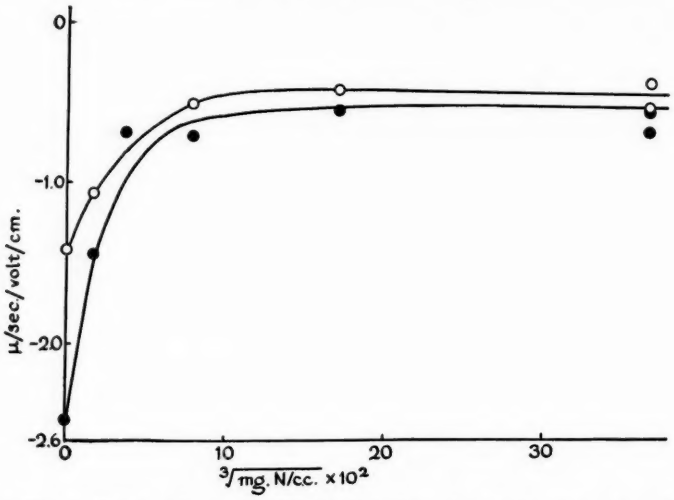

Fig. 2.—The ordinate values are electric mobility; the abscissa gives total nitrogen per c.c. of dialyzed extracts. As the concentration of nitrogen is increased, the electric mobility of the oil droplets (closed circles) approaches and becomes equal to the electric mobility of the quartz particles (open circles). This indicates that the surfaces of both quartz and oil, although differing in the absence of ragweed solution, become essentially the same when coated with ragweed films.

of the nature of the surface. For this reason, typical hydrophilic and hydrophobic surfaces were compared in the following way: Mobility measurements were made on solutions containing increasing quantities of pollen extract in 0.02 molar acetate buffer at pH 5.0, using both quartz and mineral oil surfaces. In Fig. 2 the initial electric mobility of the quartz particles in the absence of proteins is about 1.4 microns per second, the paraffin droplets moving about 1 micron faster in the same electrical field. However, as the crude ragweed extract is added in increasing quantities to suspensions of these particles, the electrical mobilities of the particles change remarkably in the following ways: Both the mineral oil and the quartz particles decrease in mobility and

near a concentration of 0.007 mg. N per c.c. the curves meet and flatten out. Within the limits of error they then take precisely the same course, running essentially horizontal independent of any further addition of the ragweed solution. We have then the phenomenon of very different surfaces of quartz and paraffin oil in the presence of ragweed extract assuming identical surface properties.

As an example of the identity of the quartz and paraffin surfaces, the actual experimental protocols are given in Table I. Quartz and mineral oil suspensions were added separately to portions of the same pollen extract. After an interval of fifteen minutes, the two solutions were mixed and mobility measurements were made on the mixture. The perfect sphericity of the mineral oil droplets made it easy to distinguish them from the quartz particles. Oil droplets and quartz particles were timed in the same microscopic field, using the same electric field strength. The average for mineral oil was 10.6 seconds, and the average for quartz particles was 10.0 seconds (Table I), identical within the limits of error for systems as difficult to measure as these. In fact, the slight difference shown in Fig 2 and in Table I is apparently not significant, for direct observation readily confirms the fact that the differences are even less than that indicated. These particles showing aberrant behavior apparently do not absorb proteins in the usual way.

TABLE I

TIMES IN SECONDS TO MOVE UNIT DISTANCE UNDER UNIT FIELD

SEPARATE		MIXED	
QUARTZ	OIL	QUARTZ	OIL
11.4	11.0	10.3	10.2
12.7	9.7	9.8	10.7
10.4	10.9	9.2	13.0
12.2	9.7	12.0	10.6
9.9	9.5	8.4	11.1
9.2	14.3	10.9	10.3
9.8	11.8	8.9	11.0
11.4	11.0	9.3	9.6
11.8	10.7	8.8	11.2
10.4	9.7	10.4	11.7
		11.3	12.0
		11.2	9.5
		9.3	9.0
		9.5	9.0
Average 10.92	10.83	10.00	10.64

TABLE II

SUMMARY OF MEANS

PARTICLE	EXPERIMENT	TIME, SECONDS	STANDARD ERROR	NUMBER OF PARTICLES
Quartz	Separate	10.92	0.36	10
Oil	Separate	10.83	0.27	10
Quartz	Mixed	10.00	0.29	14
Oil	Mixed	10.64	0.31	14

(b) *Effect of Varying the pH.*—In Fig. 3 are the data for experiments on quartz particles exposed to varying concentration of pollen extract in 0.02 molar acetate buffers. Notice that in the absence of extract, the quartz particles are negatively charged at pH 3.5, pH 4.5, and pH 5.5. As the nitrogen concentration increases, however, the mobilities of the quartz particles suspended in the solution at pH 3.5 rapidly cross the line of zero mobility and assume a positive charge. As in Fig. 2, addition of further extracts results in the flattening out of the curves with the apparent formation of a complete adsorbed film. The fact that the particles are reversed in sign of charge in acid solution indicates that the adsorbed film is amphoteric in nature, and probably protein, in view of its solubility in water, and the fact

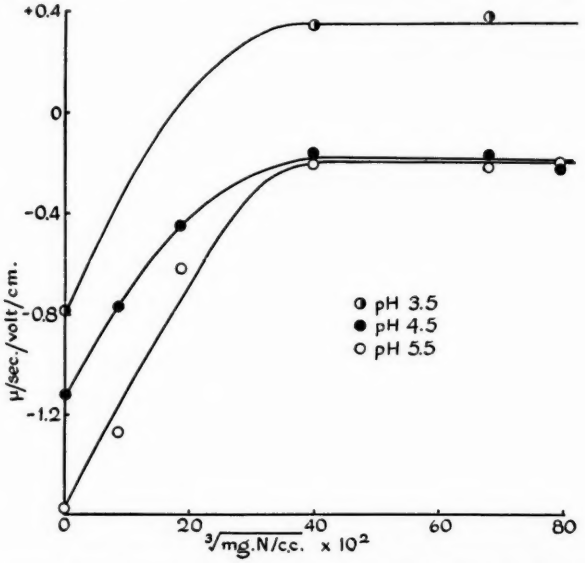

Fig. 3.—In these experiments quartz particles were studied at different values of pH with the concentration of total nitrogen increasing. Observe that the quartz particles are reversed in sign of charge at pH 3.5 if the nitrogen content of the solution is sufficiently high. This is characteristic of most protein-like surfaces.

that most or all of the low molecular weight substances in the extract were removed by dialysis. The data given in Fig. 3 were the first data obtained from the first crude dialyzed extract before considerable denaturation occurred on standing. These experiments showed that the adsorbed amphoteric film behaves very much like other adsorbed protein films, complete protein films being readily obtained. Considering the probable complexity of the mixture composing this crude ragweed extract, it is remarkable that such uniform data were obtained. Either the quartz and the paraffin oil adsorbed only one of the amphoteric constituents from the crude ragweed extracts, or else a remarkably uniform mixture of crude amphoteric material produced the film. If a mixture was adsorbed, the uniformity of the sur-

faces and constancy of the results depicted in Fig. 3 would indicate that whatever amphoteric mixture is adsorbed, is capable of being studied by this procedure.

(c) *The Mobility-pH Curves.*—As is well known, in simple aqueous solution ragweed extracts occasionally change on standing with formation of a precipitate. It was also found that the isoelectric point and the mobility-pH curves shifted to higher values of pH as the solutions were allowed to stand in the icebox. Thus the isoelectric point of the extract given in Fig. 2 was apparently 3.9, but after standing about two weeks, with consequent precipitation, the isoelectric point had shifted corresponding to the point found in subsequent experiments. Dr. Arthur Stull has informed us that he has found that the formation of the precipitate may not be related completely to the activity of the solution in alkaline or neutral media. The curves

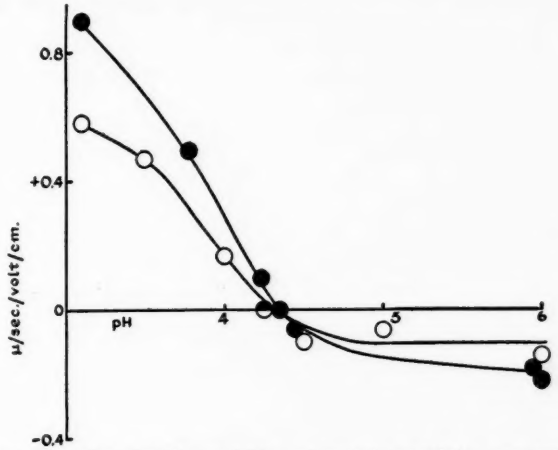

Fig. 4.—Curves for the electric mobility of quartz particles covered with ragweed solutions at different values of pH. The closed circles represent experiments at a lower salt concentration. These curves are typical of protein-coated quartz particles.

given in Fig. 4 are characteristic of aqueous extracts or sodium acetate extracts. The aqueous extract was dialyzed three days and stood in the refrigerator three days before measurements were made. Mobilities were performed in 0.02 molar sodium acetate buffers with the clear sedimented, but uncentrifuged, solution. Mobilities of particles in the acetate extract were measured one day after extraction, the final concentration of the acetate being 0.005 molar. In Fig. 4 it appears that the quartz particles when completely covered by the adsorbed amphoteric constituents of the ragweed extract, acted as if they had typical protein surfaces with isoelectric points quite close to pH 4.3. In view of the fact that the mobilities are extremely low on the alkaline side of the isoelectric point, the heights of the smooth curves cannot be readily compared. On the acid side of the isoelectric point the mobility increases as the salt concentration is decreased. This is typical of protein surfaces.[10]

(d) *Titration Curve.*—In Fig. 5 is the titration curve of a sample of the aqueous extract (dialyzed). The values are for acid and base bound per unit quantity of total nitrogen (which was practically all protein nitrogen). The solution acts as an amphoteric solution with a maximum acid combining capacity being approached at approximately pH 2.6. The slope of the curve on the alkaline side of the isoelectric point is rather low compared with the acid side. The same phenomenon is observed in the mobility-pH curves and is characteristic of proteins and of substances with overlapping dissociation constants. Although the rate of change of mobility with pH and of acid binding with pH are comparable, the two curves cannot be superimposed. Perhaps if the titration curve and the mobility were obtained in solutions of the same ionic strength, the correspondence would be better. It is more likely, however, that the titration curve includes those constituents of the crude ragweed extract which are not readily adsorbed by

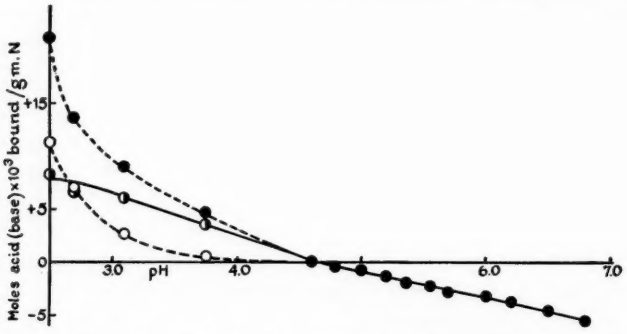

Fig. 5.—The continuous curve is the corrected titration curve of a sample of dialyzed ragweed extract. It is typical of the curves obtained with proteins or protein-like substances.

quartz. The quartz probably shows a high selectivity in taking out substances more like the proteins, while the titration curve includes any substances of lower molecular weights as well, which dissociate as acid or base. In spite of the presence of these constituents, the close correspondence between the pH of the crude ragweed solutions (pH 4.4 and 5.0) and the isoelectric point of solutions indicates that the main ionizing constituents are probably related very closely to the material adsorbed by the quartz.

DISCUSSION

Recent electrophoretic methods developed, especially by Tiselius,[11] for the fractionation and separation of the immune bodies in serum, and by Theorell,[12] for the isolation of the respiratory pigments, make use of the fact that certain proteins, e.g., serum proteins, are negatively charged under normal conditions. Since the different constituents of mixtures which were investigated have different mobilities in the electrical field, separation was possible. The data given in the

foregoing indicate that the electrophoretic method is in all probability readily adaptable to the isolation of the skin reactive constituents which have been studied here after adsorption. It is also possible that adsorption of the skin reactive constituent on inert surfaces like quartz and subsequent elution may serve as a possible method of isolation.

Other properties of allergenic solutions may be connected with the electric charge. Thus the change in isoelectric point from pH 3.9 to 4.3, observed several days after preparation, may be connected with spontaneous denaturation of dissolved protein, although we have no evidence on this point. Whether the shift to a higher pH would be observed with an additional subsequent decrease in skin reactivity remains to be investigated.

The fact that three surfaces as different as quartz, paraffin oil, and collodion, adsorb essentially the same constituent makes this method of investigation of the properties of other allergenic pollen solutions a readily available procedure which may characterize these allergens from the physicochemical point of view.

In view of the fact that the work of Cooke, Stull, and their coworkers has shown that dialyzed extracts gave skin reactions comparable with those obtained with undialyzed extracts, it is evident that a substance of high molecular weight must be responsible for the skin reactions observed in their experiments. Of course, the active group per se may be a group of low molecular weight bound to the protein, but this argument has very little to do with the point in question; for if the prosthetic group or haptene responsible for the skin reaction is so firmly bound to the large molecule remaining in the sac after diffusion that it does not dialyze out of the sac, it is to all intents and purposes part of the large molecule itself as extracted from the pollen.

It has been shown here that inactivation of ragweed pollen extract by surfaces results in a deposit on the surface of an amphoteric substance having all of the characteristics commonly observed for proteins. We, therefore, believe that the evidence presented here supports the point of view that an important active constituent of ragweed extracts is protein-like in nature.

SUMMARY

1. The electrical properties of quartz particles covered with material adsorbed from ragweed extracts are those typical of ampholytes.

2. The isoelectric point of these particles covered with a fresh extract was at pH 3.9. On standing this shifted to pH 4.3 where it was stabilized for some time.

3. Experiments with paraffin oil and collodion particles showed that these particles acquired similar amphoteric surface properties in ragweed extracts, corresponding exactly with those found when the adsorbent was quartz.

4. The titration curves of ragweed extracts were typical of solutions of proteins with a maximum acid-binding capacity near pH 2.6.

5. The data obtained are evidence supporting the point of view that the skin reactive constituent in ragweed extracts is protein-like in nature.

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ALLERGY TO GRAIN DUSTS AND SMUTS*

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THE frequency with which we have seen respiratory allergy due to inhalation of grain dust has lead to the conclusion that this is a more common condition among farmers, farmers' children, millers, and others than heretofore realized. It is the purpose of this paper to call attention to a group of 13 patients whose symptoms of asthma or hay fever are primarily caused by, or aggravated by, exposure to grain dusts and who manifest skin hypersensitiveness to grain dusts and grain smuts; and to call attention to an apparent relationship of grain smuts to grain dusts. Experience has indicated that this form of allergy, although for the most part occupational among handlers of various grains, may be a factor among city dwellers as well. Investigation in progress would indicate the importance of grain smuts in the production of grain dusts.[1]

Although cases of asthma, bronchitis, hay fever, and dermatitis, directly attributable to allergy to grain dusts have occasionally been observed, little has been written on this subject. Duke[2] observed 4 cases of wheat millers' asthma in 1935. He considered the causative factor to be either a foreign body reaction or a sensitization reaction to the small sharp wheat hairs or outer cells that fill the air during the first cleaning of wheat. He obtained positive skin tests with a 1 per cent extract of the grain dust and was able to passively transfer this sensitization to normal skins. His results in treatment, however were not favorable.

The writer[3] reported 12 cases of respiratory allergy due to molds; in 2 of these cases marked hypersensitiveness to grain dusts was noted.

Wilson[4] ascribed 3 cases of *Dermatitis venenata* to grain dust. One case,[5] a 41-year-old farmer, gave positive patch tests to corn dust and to corn oil. No other testing was done in these cases.

Wittich and Stakman[6] recently reported a case of asthma due to grain smuts. This was a 48-year-old power company worker who developed asthma whenever his work brought him into the dusty environment of Minneapolis wheat mills. Smut spores were found in his sputum and positive skin reactions were obtained to most of the grain smuts.

The recital of the latter case aroused the suspicion that the so-called wheat millers' asthma or threshers' asthma might be due to grain smuts.

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The conception of fungi as a causative factor in grain dust allergy is not new, Cadham[7] in 1924 described asthma due to rusts. In fact, Blackley[8] in 1880 suspected molds to be an exciting factor in grains and actually isolated *Chaetomium* from a grain sample. Feinberg,[9] in discussing allergy to fungi, speaks of attacks occurring in a hayloft. In several replies to occasional inquiry in Queries and Minor Notes in the *Journal of the American Medical Association,* relative to effects of grain dust, reference is made to Kober and Hayhurst's *Industrial Health.*[10] These writers refer to pulmonary injuries attributed to inhalation of grain dusts, among them atelectasis, asthma, bronchitis, and pneumonia. Kober considers these conditions either "due to intoxication from the grain protein or a contained fungus, or to an irritation from inorganic dust present in the grain."

MICROSCOPIC EXAMINATION OF GRAIN DUST

Grossly there is nothing especially characteristic about the grain dusts under discussion, except that usually they do not contain smut balls. However, in practically every sample of wheat dust or oat dust, one may find fungus spores. Microscopically, about the only difference apparent between so-called "clean" wheat dust and "musty" wheat dust is in the number of such spores found, much larger quantities being found in musty wheat or oat dust. We have observed small, round, copper-colored *Ustilago* spores, measuring about one-third the size of a ragweed pollen. In the musty grain have been observed the larger *Tilletia* spores whose echinulations make them resemble ragweed pollen. These spores have been previously observed in grain dust,[11, 13] and on pollen slides.[12] The above findings are in contrast to the findings of so-called smutty wheat or oats. Here the grain is replaced by a ball containing literally billions of smut spores.

Spores of *Alternaria* and *Helminthosporium* have been identified in these dusts, and some importance placed on the roles they play in the production of grain dust. Three factors tend to associate *Alternaria* and *Helminthosporium* with grain dust allergy. First, the spores of both these fungi are frequently found in grain dust samples. Second, the geographic distribution of *Alternaria* coincides quite well with the mid-western wheat growing belt. Third, a fair proportion (5 of 13) grain dust patients reacted strongly to *Alternaria* and *Helminthosporium.* This questionable relationship has been investigated and will be discussed in detail later. This work would indicate that it is unlikely that either of these molds, commonly seen though they are in grain dust samples, is related to the wheat dust antigen or the oat dust antigen[1] inasmuch as neutralization tests between wheat dust or oat dust fail to show any immunologic relationship (i.e., any common antigen) with *Alternaria* or *Helminthosporium.*

CLINICAL OBSERVATIONS ON GRAIN DUST ALLERGY

It appears that exposure to large quantities of grain dust as in the process of cleaning wheat or in the process of threshing wheat may result in two very different types of symptoms:

1. *Irritative Symptoms.*—In some individuals a burning sensation in the throat and chest develops soon after exposure. This symptom occurs in the nonallergic, as well as in the allergic individual; and if mild, disappears in a few hours. If more severe, what is commonly called "threshing fever" may occur. Here the patient is acutely ill with fever from 102° to 104° F., with chest pain and cough.

These symptoms are especially common among nonallergic threshers and mill workers and may be explained by Duke's[2] theory of foreign body irritation due to the fine grain hairs, and should not be confused with the manifestations seen in allergic individuals.

Two wheat mill chemists have been observed who had irritative burning sensations associated with cough whenever their work brought them for a time into the wheat cleaning room. Both these patients had negative family and personal histories for allergy, and neither patient reacted to grain dusts or to grain smuts.

2. *Allergic Symptoms Due to Grain Dusts.*—Typical symptoms of hay fever or asthma around grain dusts were observed in 13 cases. In 2 farmers (Cases 1, 13), it was the only complaint, namely, asthma after exposure to grain dusts. In 4 other allergic farmers, the story of hay fever definitely aggravated around grain dusts was spontaneously offered and was a principal complaint. In the remaining cases it was an incidental finding among one doctor's son, a shipping clerk, a student, and 5 farmers' children—all of whom had typical pollen hay fever or asthma as their presenting complaint.

The usual story is that of itching, burning eyes, sneezing and running nose, or of wheezing and coughing, occurring shortly after exposure to grain dusts during the threshing season, or at any time of the year when handling grain in the barn. Burning sensation in the throat after threshing was particularly noted. This experience was reproduced in several instances by instillation of a small amount of wheat dust extract on a nasal pledget, or by spraying some of the extract into the nostril. Handling grains raises a cloud of dust which produces symptoms. Wheat dust and oat dust are equally bad offenders. Two farmers complained of the dust from "smutty" corn; one patient had asthma only during October while husking corn. Two complained of the dust of soybeans. The work on these latter grains is not completed.

Many of these allergic farmers are able to discriminate between various samples of grain. In some cases not every oat crop, for instance, produces symptoms, usually only the "musty" ones. Wheat that is clean usually causes a minimum of symptoms, or none at all, while wheat that has a granular, musty surface is dustier and causes more symptoms. In

TABLE I

RESULTS OF TESTING WITH GRAIN DUSTS AND SMUTS

CASE	AGE	HISTORY	OTHER REACTIONS	CLEAN WHEAT DUST	MUSTY WHEAT DUST	CLEAN OAT DUST	MUSTY OAT DUST	*Tilletia tritici*	*Tilletia levis*	*Ustilago tritici*	*Ustilago avenae* AND *levis*	*Ustilago zea*	*Ustilago hordei*
1. A. M. (farmer)	28	Asthma of one year's duration after threshing or fanning wheat or oats	Pollens: negative Molds: negative	++++	++++	++++	++++	0	0	++	0	0	0
2. C. W. (farmer)	17	Hay fever and asthma for past 6 years markedly aggravated by grain dusts when threshing or bagging oats or wheat, especially if grains smell "musty." Also bothered by corn fodder	Grasses and ragweed positive Marked reactions to *Alternaria*, *Helminthosporium*, *Penicillium*, *Hormodendrum*	+	++	++	++	+	0	++	+	+	0
3. E. S. (farmer)	19	Hay fever for 6 years from May to December, definitely worse when threshing or working in hay barn. Observed marked symptoms around musty oats, wheat, and corn	Grasses and and ragweed positive Marked reactions to *Alternaria*, *Helminthosporium*, *Penicillium*, *Hormodendrum*	+	++++	++	+++	++	+	++	++	+	+++
4. H. W. (farmer)	40	Hay fever during threshing season, July and August. Bothered by musty oat dust throughout the year	Molds negative	++	++	++	++++	+++	++	++	++	0	+++
5. L. R. (farmer's daughter)	19	Perennial hay fever since childhood; recalls that as child could never play in barn because of hay fever	House dust 3 plus Ragweed positive Molds negative	+	+++	+	++++	0	0	+	+	+	0

TABLE I—Cont'd

6. S. F. (farmer's son)	6	Perennial asthma for 5 years worse from June to September. Hay fever after playing around grain in barn (horse)	Pollens negative Molds negative Horse dander positive	+	++	++	+++	+	+	+	+	+	+
7. J. B. (farmer's son)	2	Perennial asthma due to house dust; asthma on three occasions after playing with grain mash	House dust 3 plus Pollens positive Molds negative	0	++	+	+	+	++	++	+	+	+
8. P. B. (shipping clerk)	24	Late summer hay fever since 9 years old. Lived on farm until 3 years ago and while there was bothered by threshing oat and corn dust. Not bothered by wheat dust	Ragweed positive Molds negative	0	0	+++	+++	0	0	0	+	++	0
9. C. W. (farmer's son)	12	Perennial hay fever definitely worse by grain dusts, especially oat dust	House dust 3 plus Molds negative	0	+	+	+	0	++	0	0	0	0
10. J. K. (farmer)	18	Perennial asthma thought to be worse after exposure to grain dusts, including soybean dust	House dust 3 plus	0	+	+	++	0	0	++	+	++	+
11. H. M. (physician's son)	14	Late summer hay fever; frequent attacks playing in barns	Ragweed 3 plus *Alternaria* 2 plus *Aspergillus fumigatus* 3 plus	0	+	+	++	0	0	++	+	++	+
12. T. R. (student)	15	Sneezing and asthmatic attacks around grain bins and threshing	Pollens positive Reactions to *Alternaria*, *Helminthosporium*, and *Hormodendrum*	++	+++	++++	++++	++	++	++	+++	+++	+++
13. I. H. (farm hand and steel worker)	33	Hay fever from July to October, especially marked during threshing. Asthma during month of October only after husking corn	Pollens negative Marked reactions to *Alternaria* and *Helminthosporium*	0	+	++	++	+	+	+	0	+	+

some instances these patients observe that the dust from recently threshed grain does not cause as much discomfort as does the same grain after aging and drying. These factors seem to point to a living substance, probably a fungus, in the grain dust.

In addition to a history of exposure to grain dusts, there are several other factors indicating that grain dusts and grain smuts are definite etiologic factors in these cases. These are (1) positive skin reactions to grain dusts and grain smuts; (2) ability to passively transfer grain dust and grain smut reactions to normal skin; (3) the occurrence of systemic reactions with grain dust extracts; (4) the ability to reproduce symptoms by instilling grain dust and smut extracts into the nose; and (5) the beneficial results of treatment in a limited number of cases.

SKIN REACTIONS TO GRAIN DUSTS AND GRAIN SMUTS

Patients were tested with various grain dusts and grain smuts both by scratch and intradermal methods. An effort was made to obtain and test with the dust of so-called clean wheat. It would appear that "clean" wheat is only relatively clean inasmuch as smut spores and mold spores could be found, although fewer in number, in clean wheat dust.

Patients were tested with the following grain dusts and grain smuts:

Grain Dusts

1. "Clean" wheat dust
2. "Musty" wheat dust
3. "Clean" oat dust
4. "Musty" oat dust

Grain Smuts

1. Wheat Smuts
   a. *Tilletia tritici*
   b. *Tilletia levis*
   c. *Ustilago tritici*
2. Oat Smuts
   a. *Ustilago avenae* and *levis*
3. Corn Smuts
   a. *Ustilago maydis*
   b. *Ustilago zea*
4. Barley Smuts
   a. *Ustilago hordei*

All 13 patients gave positive reactions when tested intradermally with extracts of wheat dust and oat dust (Table I). Most of these patients reacted to grain dusts when tested by scratch method as well. Table I shows results of testing with several dilutions up to 1:1000 by weight. It is observed that "musty" wheat and "musty" oat dusts gave much stronger reactions than the corresponding "clean" grain dusts, and this usually coincided with their histories. Case 1 (A. M.) reacted when tested with grain dusts diluted up to 1:1,000,000. When the patients were tested with nitrogen 0.01 and 0.001 mg. per cubic centimeter of these same dusts, the reactions were more nearly equal. Table II shows, however, that the nitrogen content of the musty grains was from three to five times that of clean grains. Experience in testing with numerous grain dust extracts indicates that the potency of the extract is proportional to its nitrogen content.

It was early observed that in practically every case reacting to grain dusts, reactions were also obtained to one or more grain smuts (Table I). Ten of the 13 patients reacted to *Ustilago tritici* (wheat smut). Numerous reactions were obtained to the other grain smuts. Five of these cases also reacted to numerous mold spores, e.g., *Alternaria, Helminthosporium, Chaetomium, Hormodendrum.* Only 4 of the cases gave positive skin reactions to oat and wheat (cereal) extracts, and in only 2 cases could this reagin be transferred to the normal skin; while in no case was there any indication of inability to tolerate these grains when ingested.

Occasional nonspecific reactions were obtained with undialyzed grain dust extracts on control cases; these were rarely seen after the extracts were dialyzed. Reactions were usually obtained in patients allergic to wheat or oat (cereal).

PREPARATION OF EXTRACTS OF GRAIN DUSTS

The "clean" wheat dust extract was obtained from Dr. Myron Weitz. The "musty" wheat dust and both oat dust extracts were made by defatting with water-free ether and then extracting in Coca's solution for forty-eight hours to make a 10 per cent solution. It was then paper filtered and filtered through a Seitz filter. Cultures were taken and nitrogen determinations obtained. Because of the uncertainty of what we were dealing with in grain dust extracts, no dialysis was attempted at first. Later the extracts were dialyzed and it was found that as much as four-fifths of the protein content was lost through dialysis. Although extracts were all 10 per cent extracts, considerable variation in total nitrogen content was noted (Table II). The nitrogen content of "musty" grain extracts is three to five times that of clean grain extracts.

TABLE II

TOTAL NITROGEN IN MG. PER C.C. OF 10 PER CENT GRAIN DUST EXTRACT

	TOTAL NITROGEN
1. "Clean" wheat dust	0.10 mg.
2. "Musty" wheat dust	0.57 mg.
3. "Clean" oat dust	0.71 mg.
4. "Musty" oat dust	1.71 mg.

PASSIVE TRANSFERS OF GRAIN DUST AND GRAIN SMUT REAGINS

The reagins of wheat dust and oat dust were successfully transferred to the normal skin by the Prausnitz-Küstner method in every case attempted (7). The reagins of the grain smuts were also transferable with the same (7) sera, although not every smut reaction could be successfully transferred. *Ustilago tritici* was transferable in every case but two (Table III).

TABLE III

TRANSFERABILITY OF GRAIN DUST AND GRAIN SMUTS. RESULTS OF PASSIVELY SENSITIZING NORMAL SKIN WITH REAGINS TO GRAIN DUSTS AND GRAIN SMUTS

CASE	WHEAT DUST	OAT DUST	*Tilletia tritici*	*Tilletia levis*	*Ustilago tritici*	*Ustilago avenae* AND *levis*	*Ustilago zea*
1 (A. M.)	+	+	–	–	+	–	–
2 (C. W.)	+	+	+	?	+	+	+
3 (E. S.)	+	+	0	+	+	0	0
4 (L. R.)	+	+	–	–	+	+	+
5 (S. F.)	+	+	?	0	?	?	0
12 (T. R.)	+	+	+	+	+	+	+
13 (I. H.)	+	+	0	0	0	+	0

+Positive skin tests definitely transferable to normal skin.
?Positive skin tests questionably transferable to normal skin.
0Positive skin tests not transferable to normal skin.
–Skin tests negative on direct testing; no transfers attempted.

SYSTEMIC REACTIONS WITH GRAIN DUST EXTRACTS

Systemic reactions with grain dust extracts have been infrequent but do occur. When treatment with oat dust and wheat dust extracts was initiated in Case 1, attacks of asthma were produced with small doses of a 1:10,000 dilution on three occasions.

REPRODUCTION OF SYMPTOMS WITH GRAIN DUST AND GRAIN SMUT EXTRACTS

In an effort to prove the etiologic relationship of grain dusts and smuts to these patients' hay fever and asthma, nasal tests were tried in a limited number of cases. The technique consisted of placing a few drops of the concentrated grain dust extract (wheat dust extract was usually used) on a small piece of sterile cotton pledget, and this was gently inserted under the inferior turbinate.* Precaution was taken to observe that the mucosa appeared to be normal and that the passage was clear. The same was done with smuts. The latter were tested in dry and liquid state, usually using a mixture of three wheat smuts to simplify testing. The results of the nasal tests are shown in Table IV. Of 5 patients tested, symptoms could be reproduced in 4 with wheat dust, whereas symptoms could be reproduced in 3 cases with smuts. The patient (A. M.) whose symptoms could not be reproduced by insufflation with grain dust had been successfully treated with wheat dust extract for eighteen months to the extent that he no longer responded to exposure to grain dust in his barn nor to the 10 per cent grain dust extract sprayed into his trachea. Eighteen months previously this patient had several constitutional reactions when treated with a 1:10,000 dilution.

Both patients (E. S. and A. M.) whose symptoms could not be reproduced with instillation of smut extracts or smut powders had been successfully treated (with wheat dust extract) for three and eighteen months, respectively. A typical positive nasal test resulted in a reproduction of the patient's condition, e.g., the patient usually began to sneeze

*Extracts were later sprayed into nose or trachea.

TABLE IV

REPRODUCTION OF SYMPTOMS WITH GRAIN DUST AND SMUT EXTRACTS. RESULTS OF NASAL TESTS

PATIENT	RESULTS OF NASAL TEST WITH GRAIN DUST EXTRACT	RESULTS OF NASAL TEST WITH WHEAT SMUT EXTRACTS
1 (A. M.) (Tests performed after 18 mo. treatment with wheat dust extract)	Negative test: Concentrated oat dust extract was sprayed into nose and into trachea. No effect in 30 minutes. No delayed effect	Negative test: 0.4 c.c. of 3 per cent *Ustilago tritici* extract sprayed into left nostril. No change in mucous membrane. A few coughs resulted but no asthma occurred within 30 minutes
2 (C. W.)	Positive test: 15 min. after 0.50 c.c. of conc. wheat extract was sprayed into left nostril, eyes became congested and itchy, *throat became itchy* and left inferior turbinate became moderately edematous	Positive test: 5 minutes after instillation of mixed powdered wheat smuts, eyes became red and inflamed. Left inferior turbinate became edematous and boggy, with complete closure of passage
3 (E. S.) (Tests performed after 3 mo. treatment with wheat dust extract)	Positive test: Inferior turbinate became markedly edematous and pale with complete closure of passage within 15 min. Complained of itching of nose and left eye and of burning sensation in throat	Negative test: Liquid and powdered smut extracts caused no change in nasal mucosa
9 (C. W.)	Positive test: Eyes became watery and inferior turbinate became extremely edematous and pale within 10 min. Much sneezing occurred within 10 min. of instillation of 10 per cent wheat dust extract	Positive test: Eyes became watery; itching in nose; left inferior turbinate moderately edematous and pale; air passage occluded within 15 min. of instillation of mixed powdered wheat smuts
12 (T. R.)	Positive test: 5 min. after spraying right nostril with wheat dust extract, eyes and nose became watery, inferior turbinate became moderately edematous	Positive test: Nasal pack containing mixed smut extracts inserted for 5 min. In 12 min. repeated paroxysms of sneezing occurred; eyes became red and watery. Turbinate became edematous and passage obstructed

within ten to fifteen minutes, the eye became injected, and the inferior turbinate became so edematous and pale as to close the nasal passage in the affected side. Two patients complained of itching and burning of the throat and volunteered that "it felt as though I was in grain dust." Compared to the reactions obtained with wheat dust extract the results with smut extracts were as a whole milder. All tests on allergic controls and normal controls were negative.

COMMENT

What is the relationship then between wheat dust and wheat smuts? Between oat dust and oat smuts? The concomitant allergy to grain dusts and grain smuts cannot be overlooked. The ease and frequency with which allergic symptoms can be reproduced by nasal instillation with both grain dusts and grain smuts is striking. Neutralization tests to be reported between grain dusts and grain smuts indicate a common factor between the two.[1]

What constitutes the difference between clean grain dust and musty grain dust? The latter are much more powerful antigens, and their extracts have a higher nitrogen content. What has produced this change? Apparently not molds according to evidence to be presented. More likely it is that smuts are related in some way to this process. It is important to recognize that despite the apparent relationship between smut antigen and grain dust antigen, a wheat dust extract is by no means identical with a wheat smut extract. Moreover, our grain dusts do not contain smut balls, although smut spores can be readily identified microscopically. However, it would appear that it is not so much the smut itself to which these patients have become allergic, although this too has happened, but more likely they are allergic to a by-product or an end product of the action of the smut of the grain itself to form what we call grain dust.

CONCLUSION

1. A series of 13 cases of respiratory allergy due to grain dusts and grain smuts is reported.

2. Various clinical observations are described.

3. The evidence indicating etiologic relationship of grain dusts and grain smuts to these cases includes:

   (a) History of asthma or hay fever after exposure to grain dusts, especially to musty grain dust.

   (b) Positive skin tests, both dermally and intradermally, to grain dusts and grain smuts.

   (c) Presence of transferable reagins to grain dusts in every case and to one or more grain smuts in every case.

   (d) Occasional constitutional reactions with use of grain dust extracts subcutaneously.

   (e) Successful reproduction of symptoms by instillation of grain dust or various grain smuts into untreated patients' nostrils.

4. The possible relationship of smuts to the production of the grain dust antigen is suggested.

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AN ANALYSIS OF THE COMPARATIVE RESULTS OF SKIN TESTING WITH COOKED AND UNCOOKED FOODS*

Preliminary Report

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MANY writers have offered various explanations for the failure to obtain positive food reactions in the presence of positive clinical histories of food hypersensitiveness. Also, the presence of positive food reactions by skin test has been difficult to explain in the presence of negative clinical histories. Walzer[1] emphasizes the fact that skin tests are usually performed with extracts prepared from raw foods, but cooking may so alter the nature of many ingestants as to render them harmless even to the sensitive individual. Tuft[2] comments on the failure of clinical confirmation of positive food skin tests with the statement that the effect of temperature upon allergens with some patients may so alter the character of the allergen as to render it inert, whereas in other instances boiling may have little or no effect. Feinberg[3] contends that modification (i.e., by heat) of a food will at times decrease its allergenic quality so that sensitive individuals may tolerate it. Brown[4] states that it has been found repeatedly that persons may safely eat food after prolonged cooking which, when raw or only cooked for a few moments, they were not able to eat without untoward results. In children, particularly, food tests, especially when positive, have been accepted as yielding pertinent information, and yet Chobot[5] maintains that there is a wide variation in the clinical value of information obtained from direct skin testing in food sensitive children. Many children give positive direct skin tests without corresponding clinical sensitiveness, although the reverse is also frequently true. Ratner and Gruehl,[6] through their experimentation with evaporated or superheated milk, show an unmistakable loss of antigenic properties of the whey fraction. They feel the loss of the antigenic properties of heated milk is presumably due to coagulation of the whey proteins. The same authors[7] found dextrimaltose and corn syrup nonanaphylactogenic. Here again the loss of antigenic properties is attributed to the superheating necessary in the preparation of these products. Chick and Martin[8] studied the process of heat coagulation with solutions of crystallized egg albumen and were able to show that egg white, when heated, is reduced in antigenicity. Schloss,[9] however, in 1912 by scratch testing with heated solutions of ovomucoid and the proteoses, almond and oats, using the original (unheated) solu-

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tion as a control, found no perceptible difference in reactions. To further demonstrate the complexity of this problem and the resulting difficulty in attempting to prognosticate the effect of cooking on the allergenicity of foods, Prausnitz and Küstner[10] were able to illustrate in the case of one of the authors (K), a marked sensitivity to cooked fish and none to raw fish. Ratner[11] concludes from these conflicting facts that in the absence of specific information pertaining to the diminished antigenicity of foods, no generalization can be made with reference to the influence of heat on all foods.

The frequent failure of confirming positive skin tests to foods with clinical trial has been explained by the fact that, whereas skin tests had been made with extracts of foods prepared from the raw state, the clinical experiments were done with foods cooked for varying lengths of time. A search of the literature has failed to reveal any reports that would seem to confirm this fact. With this problem in mind we prepared a fairly representative group of food extracts in both the raw and cooked states; this group includes foods that are eaten both cooked and raw. All tests were made on a group of allergic individuals who are under treatment for various allergic manifestations, e.g., bronchial asthma, hay fever, allergic rhinitis, and urticaria. No attempt was made at this time to correlate our findings with clinical tests, as it seemed most important as a preliminary step to note variations, if any, in the skin response to the test of each food in the raw and cooked state.

METHOD

Seven allergens were prepared in the routine manner in both the raw and cooked states, and their total nitrogen content was determined by the Kjeldahl method. The list included: cabbage, egg, onion, celery, carrot, white potato, and string bean.

Celery, cabbage, and onion are frequently eaten in the raw state, and egg and carrot occasionally, while potato and string bean are eaten cooked.

The raw extracts were prepared by extraction in buffered saline solution, dialyzed for seven days, and sterilized by Berkefeld filtration. They were all standardized by the determination of total nitrogen content, except for egg which was diluted 1:1000 with buffered saline solution. In general, the process of extracting cooked vegetables duplicated that of the raw, except for the process of cooking. Each food was cooked in closed vessels, using buffered saline in place of water. This practically eliminated any loss of content through evaporation. Buffered saline was used since it does not deteriorate with boiling and is also feasible for the extraction of the food during the process of cooking.

Where the total nitrogen differed greatly in the two states, the extracts were reduced to the concentration of that of raw food extract wherever possible.

All testing was done by the intracutaneous method on the upper and outer aspect of the arm, with the raw extract opposite the cooked to facilitate more accurate comparison. Readings were taken at the end of ten and twenty minutes. Recipients were taken at random from the attendance of the allergy clinic. All were allergic, although manifestations of their sensitivity varied. The amount of extract injected was about 0.02 c.c., and in every case complete testing of each individual was done at one sitting.

RESULTS

The results of our tests are summarized in Table I. Only distinct variations in reaction were noted. In cases of doubt the tests were repeated.

TABLE I

COMPARISON OF SKIN TESTS WITH RAW AND COOKED FOODS

ALLERGEN	NO. OF PAIRS OF TESTS	REACTIONS EQUAL	REACTIONS UNEQUAL	
			RAW > COOKED	COOKED > RAW
Cabbage	113	101 (89 per cent)	7 (6.1 per cent)	5 (4.4 per cent)
Egg	106	102 (96 per cent)	1 (0.9 per cent)	3 (2.8 per cent)
Onion	106	95 (89 per cent)	3 (2.8 per cent)	8 (7.5 per cent)
Celery	105	94 (89 per cent)	5 (5.7 per cent)	6 (4.8 per cent)
Carrot	105	97 (92 per cent)	3 (2.85 per cent)	5 (5.7 per cent)
White potato	112	104 (92.5 per cent)	5 (4.5 per cent)	3 (2.7 per cent)
String bean	64	59 (92 per cent)	4 (6.2 per cent)	1 (1.5 per cent)
Total (pairs)	711	652 (91 per cent)	28 (3.9 per cent)	31 (4.3 per cent)

A slight reaction was one showing a definite, although slight, increase in the size of wheal. An increase to twice its normal size was considered a moderate reaction. A marked reaction was one which formed pseudopods. Of the 652 pairs of equal reactions, 203 pairs, or 31 per cent, were negative. The remainder were equally slight, moderate, or marked. In a small group the differences in reaction between the cooked and the raw extracts were so slight that they were considered of equal reaction. In Table I, in which are tabulated the pairs showing a greater reaction of one over the other, one of the pairs reacted either moderately or markedly against a negative reaction to the other. No attempt was made at this time to correlate the results of these tests with clinical tests to the raw or cooked food.

DISCUSSION

Over one hundred allergic individuals were studied with intradermal tests of food extracts prepared from both the raw and cooked state in an attempt to determine whether there was any noticeable and pertinent difference in the reactions thus obtained. The total number of comparisons for all the foods in our testing group numbered 711 pairs of tests (Table I). Of this number, 652 pairs, or 91.8 per cent, were considered to be equal, i.e., the resulting reaction of the test with the raw

extract was equivalent to that of the cooked extract. This group included 203 pairs in which both reactions were negative. In 28 pairs, or 3.9 per cent, the skin reaction was greater with extracts prepared from the raw state than with those prepared from the cooked state. In 31, or 4.3 per cent, the reverse was true, i.e., skin tests with cooked extracts were greater than those with raw extracts. It must be remembered that these two groups form the small percentage of tests in which there has appeared a definite difference in cutaneous response to cooked and raw extracts. It was essential, therefore, to get accurate readings of such skin reactions. In both groups, the positive reactions were moderate or marked, while the negative reactions were slight or negative.

Since skin tests are usually performed with extracts prepared from raw foods, our primary interest lies in that group where positive results were obtained on skin tests to cooked extracts, whereas slight or negative results were obtained on testing with raw extracts. If a fairly moderate percentage of the cases fell into this group, one would be compelled to feel that our present routine testing with raw extracts was inadequate and that further testing with cooked extracts was essential. However, this is not the case. Only 4.3 per cent of our cases showed this discrepancy, and when one considers the increased expense to both patient and physician, the additional time factor that would be required for these further tests, and the increased nuisance to adults and pain to children, one cannot help but feel that fortunately the results are as they are.

We feel, therefore, that routine skin testing with extracts prepared from the raw state, while often inconclusive and completely at variance with clinical tests, are adequate for the vast majority of cases.

While increased or decreased allergenicity of these foods could be demonstrated as a result of cooking in about 4 per cent of all tests, the results were not consistent, and definite conclusions could not be drawn. Since 91 per cent of all tests showed equal intradermal response to both the cooked and raw extracts, the occasional increased or decreased reaction does not signify a change in degree of allergenicity beyond that which may occur in any repetition of tests with a given extract in any one case. Certainly, the usually accepted idea that heat will destroy the allergenicity of a food is not proved by these findings—at least not by intradermal skin testing, although it may be true clinically as demonstrated in Küstner's patient, who was sensitive to cooked fish but not to raw fish.

At present we are attempting to obtain clinical confirmation of positive skin tests, from either raw or cooked extracts. In cases with positive clinical reactions further check-up with passive transfer and neutralization experiments will be done. Our results will be compiled and presented in a later paper.

CONCLUSIONS

1. A series of cases were skin tested with the extracts of foods prepared from the raw and cooked states. In this group are included foods which are eaten raw or cooked, or both raw and cooked.

2. Of 652 such pairs of tests, it was shown that 91 per cent were equal; that in only 3.9 per cent, the raw extract reacted positively against a negative cooked test; and that in 4.3 per cent, the cooked extract reacted positively against a negative raw test.

3. As a result of these observations, it may be concluded that skin testing with extracts prepared from cooked foods is not considered essential or practical.

4. As a further result of these tests, it appears that heat does not appreciably affect the allergenicity of foods, as demonstrated by intracutaneous skin tests. Changes occurring in foods as a result of cooking are so infrequently demonstrable by test that they may be ignored, except in the occasional case, in which the diagnosis is reached by the clinical application of the trial-and-error diet with raw and cooked foods.

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STUDIES IN GASTROINTESTINAL ALLERGY*

Allergy in the Pathogenesis of Peptic Ulcer

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THE existence, character, and extent of gastrointestinal allergy is a matter of fairly recent study, although isolated incidences of apparent but unrecognized visceral manifestations can be found in both lay and medical literature of some antiquity. As late as the early twentieth century, reports of gastrointestinal allergy appearing in the literature were vague. In 1904 Osler[1-3] described the frequency of visceral crises in erythematous skin diseases and Morris[4] demonstrated angioneurotic edema in bits of gastric mucosa obtained in stomach washings. It was in 1921 that Manwaring[5, 6] and his associates demonstrated how great a part the gastrointestinal tract plays in anaphylactic shock. The fundamental work of gastrointestinal allergy, that of Cooke,[7] Rowe,[8-10] Andresen,[11] Duke,[12-14] Gay,[15-17] Vaughan,[18, 19] Alvarez,[20, 21] Fries,[22] Kern,[23] Smul,[24] and many others, is all a matter of the last twenty years.

Even more recent is the conception of an allergic factor in the pathogenesis of benign peptic ulcer. Demel[25] in 1923 observed that the vascular changes in an allergic reaction and in peptic ulcer were somewhat similar and that, therefore, some ulcers might be manifestations of local anaphylaxis. He suggested the Arthus phenomenon or an urticarial wheal as the exact mechanism. Ivy and Shapiro[26] in 1925 produced lesions resembling peptic ulcer in rabbits by injecting into the gastric mucosa a foreign protein to which the animal had been previously sensitized. Working independently, Alessio[27] and Vallone[28] could not produce these results. Carr[29] in 1926 reported milk allergy in a patient with peptic ulcer. Two other such cases were reported by Sterling[30] in 1929. Kern and Stewart[23] in 1932 reported that 50 per cent of 32 patients with peptic ulcer had either personal allergy or allergy in the family. Rowe[10] has suggested that "lesions similar to canker sores could readily occur in the stomach or duodenum, and that the continued action of the digestive ferments on such sores could produce peptic ulcers of varying degrees." Gay[17] found that two-thirds of a series of 33 cases of peptic ulcer gave an

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allergic history and suggested the use of the leucopenic index as an additional aid to determine the specific food causing the ulcer. Rinkel[31] has emphasized ulcerlike symptoms in gastric allergy and Smul[24] claims to have demonstrated an allergic factor.

It is the object of this paper to report the study of one group of patients with definite allergy and a second group with definite peptic ulcer in order to ascertain whether allergy is a factor in the pathogenesis of ulcer.

THE ALLERGY GROUP

Seventy-two patients with proved allergy were used for this study. They were chosen from consecutive admissions to the allergy clinic of the Third (New York University) Medical Division of Bellevue Hospital. Patients with complicating disease or those unable to give adequate histories concerning themselves or their families were omitted. A careful history was taken of the family incidence of allergy and particularly of gastrointestinal symptoms in relatives. The patients were then questioned about any gastrointestinal symptoms they may have had in the past or at present, the duration of the attacks, and the time relationship to the allergy. All operations were studied for an allergic association. Every patient was skin-tested with the principal foods and inhalants. All were given a barium meal, and the stomach and duodenum were studied by roentgen means for organic or functional disorders. Repeated studies were made on those having positive x-ray findings.

Results.—Thirty-five, or 49 per cent, had gastrointestinal complaints of such severity as to seek the advice of the doctor or to resort to self-medication frequently for relief. The symptoms, in the order of frequency were: gas, constipation, belching, epigastric distress, epigastric pain, heartburn, vomiting, nausea, distention, and diarrhea. Nineteen of these 35 patients had symptoms which resembled closely those of an ulcer syndrome. As occurs with any group of cases with peptic ulcer, the majority had pain relieved by food or alkalies. Some had epigastric pain associated with nausea and vomiting.

TABLE I

INCIDENCE OF DEMONSTRABLE X-RAY CHANGES

	NUMBER	PER CENT
Patients with peptic ulcer by x-ray	4	5.5
Patients with localized spasm in stomach and duodenum by x-ray	8	11.0
Patients with positive x-ray findings in stomach and duodenum	12	16.5

Of the 72 patients, 60, or 83 per cent, had negative x-ray findings. Of the 12 with positive findings, 4, or 5.5 per cent, had definite duo-

denal ulcers, and 8, or 11 per cent, had either gastric or duodenal spasm. Of the 8 with spasm, repeated x-ray studies showed either normal findings or an incisura in a different location. All 12 with positive x-ray findings had a long history of gastrointestinal complaints, and were in the group of 19 patients who had symptoms resembling those of a peptic ulcer.

TABLE II

SUMMARY OF PATIENTS WITH POSITIVE X-RAY FINDINGS

NO.	AGE	SEX	FOOD IDIOSYNCRASIES	COINCIDING SKIN TESTS	ALLERGY DIAGNOSIS	X-RAY DIAGNOSIS	KNOWN ULCER	G. I. SYMPTOMS
16	46	M	0	0	Asthma	Duodenal ulcer	0	Epigastric pain
20	39	M	+	+	Asthma	Duodenal* ulcer	+	Ulcer syndrome
27	40	F	+	0	Asthma Urticaria Eczema	Duodenal ulcer	0	Ulcer syndrome
87	21	M	0	0	H. F. V. M. R.	Duodenal ulcer	+	Ulcer syndrome, hematemesis
6	16	M	0	0	Asthma	Duodenal spasm	0	Postprandial distress
19	32	M	0	0	H. F.	Duodenal spasm	0	Epigastric pain and burning
47	32	M	+	0	H. F. Urticaria	Pylorospasm	0	Heartburn
79	21	M	+	0	Asthma Urticaria	Duodenal spasm	0	Gas and belching only with hives
81	37	F	+	+	Asthma V. M. R. Urticaria	Duodenal spasm	0	Epigastric distress
85	57	M	0	0	Urticaria	Pylorospasm and incisura	0	Postprandial distress and vomiting
92	63	M	0	0	H. F.	Duodenal spasm	0	Epigastric burning and gas
99	36	M	+	+	H. F.	Duodenal spasm	0	Epigastric distress

*Operated upon for perforating duodenal ulcer in 1932.
H.F. = Hay fever.
V.M.R. = Vasomotor rhinitis.

Of the 72 patients there were 45 with asthma, 45 with hay fever, 10 with allergic rhinitis, 8 with urticaria, and 6 with eczema. Many of the patients had more than one allergic diagnosis. Of the 12 patients with positive x-ray findings in the stomach and duodenum, 6 had asthma, 5 had hay fever, 5 had urticaria and angioneurotic edema, 2 had allergic rhinitis, and 1 had eczema.

TABLE III

ALLERGY IN ULCER PATIENTS

PATIENT NO.	V. M. R.	H. F.	ASTHMA	CHRONIC COUGH	ECZEMA	URTICARIA
1	+					
2	+					
3	+			+		
4						+
5						+
6		+				
7		+				
8			+	+	+	

V.M.R. = Vasomotor rhinitis.
H.F. = Hay fever.

TABLE IV

SUMMARY OF ALLERGIC FINDINGS IN ULCER PATIENTS

NAME	FAMILY HISTORY OF ALLERGY	PERSONAL ALLERGY	EOSINOPHILE PER CENT	POSITIVE SKIN TESTS	FOOD IDIOSYNCRASIES	FOOD IDIOSYNCRASIES AND POSITIVE TESTS
E. J.	+	0	2	0	+	0
J. R.	+	0	1	0	0	0
R. R.	+	0	1	0	0	0
A. S.	+	+	0	+	+	0
J. K.	+	+	1	+	+	0
S. M.	+	+	0	+	+	0
A. L.	+	+	1	0	+	0
J. L.	0	+	1	+	0	0
W. G.	0	+	1	0	0	0
A. M.	0	+	3	0	+	0
M. G.	0	+	4	0	0	0
H. M.	0	0	0	+	+	0
J. G.	0	0	1	+	0	0
P. T.	0	0	1	+	+	+
M. H.	0	0	1	+	+	+
A. U.	0	0	0	+	+	+

THE ULCER GROUP

Seventy-five patients in the Sub-clinic of Gastroenterology of the Third Medical Division of Bellevue Hospital were used for this study. All gave suggestive ulcer histories, and the diagnosis was confirmed by x-ray examination. Consecutive cases were used, omitting those patients whose histories were doubtful from language difficulty or through lack of intelligence on the part of the patient, or where gastrointestinal or other complications were confusing.

A careful history was taken on each of the 75 patients concerning family incidence of asthma, hay fever, allergic coryza, urticaria, angioneurotic edema, migraine, and eczema. Each patient was questioned carefully for any evidence of personal allergy, past or present. Parents and other members of the family were consulted for helpful information. An eosinophile count and a physical examination, particularly of the skin, nasal passages, and the lungs, were done. Each patient was given the same routine skin tests that the allergy patients received.

Results.—Seven, or 9.3 per cent, of the 75 patients gave a family history of allergy. Eight patients, or 10.6 per cent, gave a history of some allergic manifestations at some time in life. These included 4 of the 7 patients with family allergy (Table III). Nine patients had definite skin reactions to one or more allergens. Four of these were either in the personal history or family allergy groups. Thirty-two patients, or 42.6 per cent, knew of one or more foods which always distressed them. The foods which most commonly caused symptoms in the order of frequency were: pork, cabbage, orange, cauliflower, onion, banana, turnip, apple, egg, tomato, prune, shellfish, coffee, beans, spinach, lamb, lettuce, and oatmeal. In only 3 patients did the skin test correspond to the food idiosyncrasy. The eosinophile count did not exceed the normal limits in any instance.

DISCUSSION

Eight, or slightly above 10 per cent, of 75 patients with proved peptic ulcer were found to be allergic. Figures[32] for the incidence of allergy in large groups are given as 1 to 10 per cent. Four, or 5.5 per cent, of 72 definitely allergic patients had peptic ulcers. This is well within figures for incidence in the general population given by Crohn,[33] Hurst and Stewart,[34] and Rehfuss.[35] It is concluded that allergy is not a factor in any significant proportion of peptic ulcers and that peptic ulcer is not of increased frequency in allergic groups.

Nineteen of 72 allergic patients presented symptoms which could be mistaken for that of an ulcer syndrome. On repeated roentgen studies of the stomach and duodenum, 8 of these showed transient spastic phenomena without a demonstrable niche. Gray[36] has described an ulcerlike complex as a result of an autonomic mechanism initiated by tobacco smoking or a focus of irritation, such as chronic appendicitis, or kidney stones. Our findings suggest that an allergic process can explain the occurrence of a clinical entity closely resembling an ulcer.

Among 72 allergic subjects, the allergy consisted of urticaria or angioneurotic edema in 8. Half of this group showed spastic findings in the stomach and duodenum. A fifth case of the urticaria group had duodenal ulcer. This is in line with the study of Kern and Stewart[23] who found that in a series of 32 ulcer patients, 14 had some form of personal allergy, and of these, 7, the greatest number, had urticaria. These findings seem to lend support to the explanation of Demel[25] that gastrointestinal allergy is due to an angioneurotic edemalike reaction and that the localized spasm demonstrated by x-ray may be due to, or associated with, the presence of a wheal.

SUMMARY

Seventy-five patients of proved peptic ulcer were studied for evidences of allergic manifestations, and a second group of 72 allergic individuals were studied to determine the presence of ulcer.

From these studies, we have no valid reason to assume that allergy plays an important part as an etiologic factor in peptic ulcer cases.

A small group among the allergic patients was found with ulcer-like symptoms, but without demonstrable roentgen signs of ulcer. There were spastic phenomena in the stomach or duodenum or both in each of these cases. This group showed a striking, though not constant, association with urticaria and angioneurotic edema.

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BILHARZIAL ASTHMA*

A New Type of Allergic Bronchial Asthma

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INTRODUCTION

OF THE innumerable causes of allergic bronchial asthma the helminths probably play the least important role. This condition, however, may be theoretically important. The following is a discussion of a type of allergic bronchial asthma brought about by helminths of the blood, the Trematoda: *Schistosoma haematobium and Schistosoma mansoni* (perhaps other species of this family too).

The parasites belonging to the category of *Schistosoma* are widely spread in certain countries (Egypt, South Africa, Brazil, Porto Rico, Japan, and China) and a number of diseases are known to be caused by them. In Egypt it is particularly *S. haematobium,* the parasite of bilharziasis of the bladder, and *S. mansoni,* which causes intestinal bilharziasis, that are most frequently encountered. Almost ten millions of the population of the Nile Valley suffer from bilharziasis.

Suarez (1930) was the first to report a case of bilharziasis accompanied by asthmatic attacks. Since the lungs showed bilharzial involvement in the x-ray, he considered those attacks due to the anatomic pulmonary changes and, therefore, called it "schistosomiasis of the lungs simulating bronchial asthma." Another case in which the author did not realize the nature of the disease was described by H. Brugsch[2] (1931). Based upon the author's[3, 4] description we subsequently succeeded in definitely identifying the disease as a bilharzial process with pulmonary involvement and asthmatic attacks. With observations in two further patients we recently had the opportunity of giving an outline of the picture of bilharzial asthma.[5] Having been in a position to observe another case we present this paper, based upon a total of 6 case histories, 4 of which have been observed by us.

CASE REPORTS

Case 1.—G. A., a school boy, aged 10½ years, son of a police officer, had been suffering for two years from severe attacks of febrile asthma. His temperature would rise to 40° C.; there were severe paroxysms of difficult expiration, with loud and audible whistling. There was also much cough, without expectoration. On occasions these attacks were accompanied by urticarial rashes.

Nine months previous to admission the patient had had an attack of "dysentery," but neither the microscopic examination nor the culture of the stools made in our laboratory revealed the presence of either amoebae or dysentery bacilli. Emetine

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treatment cured the disease within three months. In January, April, and May, 1934, attacks of hematuria of short duration appeared. The laboratory examinations, however, revealed only a few red blood corpuscles. No eggs of bilharzia were detected. In May, 1934, a rectal polyp with bleeding had to be removed; its histologic examination, however, was omitted.

The boy's parents, who on account of the frequent febrile attacks suspected pulmonary tuberculosis, consulted a lung specialist who was able to dispel these suspicions as unfounded. Nevertheless, it was not possible to identify the disease or carry out successful treatment. At that time the boy's condition was the same as when he was admitted to hospital on Nov. 3, 1934. He was in excellent general health. There was no fever. The lungs showed the picture of an asthmatic attack: marked emphysema, low diaphragm with little movement, hyperresonant percussion note, distant respiratory sound, prolonged expiration, and abundant wheezing everywhere.

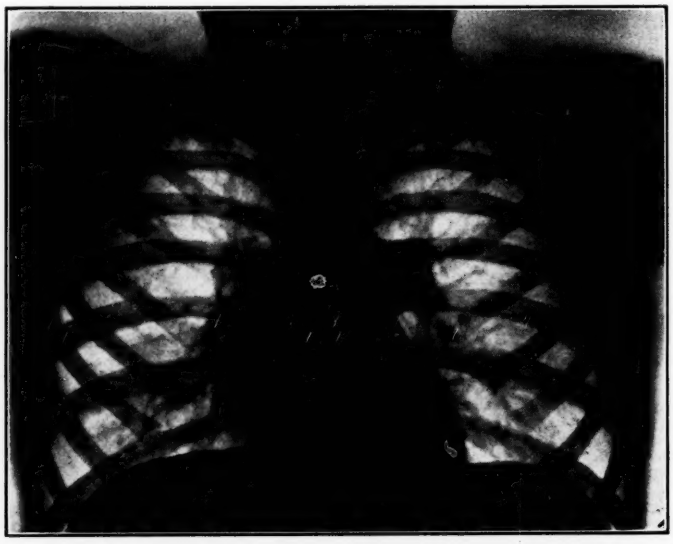

Fig. 1.

The liver as well as the spleen was markedly enlarged and firm. The liver extended below the costal margin by a hand's breadth, the spleen by the width of three fingers. On rectal examination a new polyp was palpable.

The blood picture showed—in agreement with a previous count April 26, 1934—a leucocytosis of 22,700, 30 per cent of which were mature eosinophilic cells. A few days later, 34,800 leucocytes were counted, 73 per cent of which were eosinophiles.

On microscopic and cultural examination of the blood, urine, and stools, no suggestion of a parasitic disease was found. In the sputum a large number of eosinophiles was detected, but neither pathogenic bacteria nor eggs of parasites were present.

The radiograph of the lungs taken before admission (Fig. 1) showed nothing particular, except some increase of striations and emphysema. Later radiographs showed further retrogression of the emphysema.

The assumption that this kind of asthma was caused by anaphylactogenic substances of bilharzial origin was made evident by the presence of many of the classical phenomena of bilharziasis of the bladder in spite of the failure to detect eggs in the urine or feces.

TABLE I

WHITE BLOOD CELL COUNTS OF CASE 1 (G. A.)

DATE	LEUCOCYTES	EOSINOPHILES PER CENT	REMARKS
1934			
4/26	7,500	15	
11/3	22,700	30	
11/7	34,800	73	11/8/34 to 12/6/34 treatment with neostibosan
11/16	19,600	63	
12/3	15,600	65	
12/15	17,600	49	
12/27	17,000	48	
1935			
1/2	17,100	49	
1/10	11,500	49	
1/18	17,000	40	1/3/35 to 1/23/35 treatment with fuadin (35 c.c.)
1/26	10,100	38	
2/2	10,500	23	
2/9	6,500	18	
2/16	6,900	20	
2/23	5,000	11	
3/2	4,800	23	
3/9	7,500	20	
3/16	6,500	14	
3/23	7,400	29	
4/13	6,200	19	
4/20	5,800	29	
4/27	6,800	30	
5/4	8,300	34	
5/11	9,100	46	
5/18	16,900	42	
5/25	12,900	50	
6/1	15,600	58	
6/8	12,200	38	
6/17	20,000	64	6/13/35 to 6/25/35 treatment with fuadin (35 c.c.)
6/25	15,700	54	
6/29	14,200	52	
7/6	12,000	52	
7/13	15,700	46	
7/20	9,500	47	
7/27	6,500	25	
8/3	6,100	24	
8/17	5,700	10	
8/31	5,400	14	
9/7	8,300	12	
9/14	5,200	7	
9/21	5,800	7	
10/5	5,100	16	
10/19	5,700	24	
10/29	5,200	10	
11/25	5,600	11	
12/11	7,000	6	
12/14	5,500	8	
1936			
1/30	5,800	2	

The pathognomonic hematuria and the dysentery, which was favorably influenced by emetine in spite of absence of amoebae, eosinophilia, and urticaria (as have been described as typical of the initial stage of schistosomiasis), enlargement of liver and spleen which occur, as a rule, in the type of infection occurring in the Far East, as well as repeated formation of intestinal polypi, are all characteristic of intestinal bilharziasis.

In view of these facts antimony was given, followed by neostibosan, and later fuadin in two series, the latter being incomplete.

The asthmatic attacks definitely disappeared from the beginning of the first series of injections. Urticaria occurred several times between the first and second series, but not again afterwards. The liver and spleen regained their normal size, the blood picture approached normal, a somewhat increased number of eosinophilic cells persisting as usual, while the total leucocyte count became normal.

Summary.—Case 1 is one of bilharziasis of the bladder and intestine accompanied by marked enlargement of liver and spleen and a high degree of eosinophilia. Eggs of parasites could not be detected either in the urine or in the stools. Adequate antimony treatment effected complete cure.

The disappearance of the asthmatic attacks effected by the antimony therapy proves that these were a consequence of the bilharzia infection. That they were not due to pulmonary involvement by the parasite, i.e., a local disease of the lungs, is shown by two facts: (1) The x-ray (Fig. 1) reveals the lungs to be free from bilharzia foci. (2) Urticaria disappeared under specific bilharzia therapy.

CASE 2.—A. J., a boy, aged 14 years, had no peculiarities in the family history and no important previous diseases. He had been suffering for five years from periodically recurring severe asthmatic attacks. In spite of thorough questioning no information could be obtained concerning a bilharzia infection of the bladder or intestine.

The boy was markedly backward in growth, possessed a pale coffee-brown color, and showed evidence of poor nutrition. He was first seen during a severe asthmatic paroxysm with high degree of emphysema and marked expiratory dyspnea. The liver extended three fingerbreadths below the costal margin and its consistency was increased. The spleen was firm and pushed hard against the hand on inspiration.

On account of the combination of asthma and enlargement of liver and spleen it was possible to make a clinical diagnosis of bilharzial asthma.

Eggs of parasites could not be found either in the stools or in the urine.

The x-ray picture of the lungs (Fig. 2) showed, in addition to a high degree of emphysema, increased striations and, especially on the right near the hilum and in the inferior lobe, a number of irregularly outlined foci, varying in size from that of a pea to that of a bean. Some of these foci were confluent or joined together by the striations, thus casting a very soft shadow.

The blood cell count showed a leucocytosis of 14,900, of which 64 per cent were eosinophiles. The intradermal reaction with liver extract of infected snails (Fairley reaction) was positive.

The first course of antimony was given from November 22 (30 c.c. fuadin). After no more than three injections, the status asthmaticus which had lasted for twenty days improved progressively. A week later all subjective difficulty in breathing had disappeared. During this period, as has been our invariable experience, the blood count showed at the beginning of the treatment a further increase both of the total leucocyte count and of the proportion of eosinophiles. The liver and spleen regained their normal size. From December 7 to December 22 a further course of antimony was given (30 c.c. fuadin). Occasionally during this period some musical râles were heard. Subjectively, the patient felt well and respiration was normal. He was able to take part in gymnastic lessons at school. At that time the general condition improved greatly. The body weight increased from 38.5 kg.

to 41 kg. During December the total leucocyte count became normal; the number of eosinophiles also decreased, but remained stationary at a level of 30 to 40 per cent. In spite of the disappearance of the asthmatic manifestations, a second radiograph showed that the condition of the lungs was quite unchanged.

During the first half of January and more so in the second half, the blood began to approach the figures obtained at the beginning. Early in February the liver and spleen were once more enlarged. During the last week of January bronchial asthma reappeared. Pulmonary emphysema also increased, but the symptoms, both subjective and objective, did not reach the degree of severity seen at the beginning. During the first half of February the frequency as well as the severity of the asthmatic attacks increased, finally resulting in status asthmaticus. The nights particularly were unbearable for the patient. Both liver and spleen were enlarged again. The total leucocyte count rose to about 20,000. From February 18 to March 18, 1938, a course of fuadin was given (48 c.c.). After no more than three injections, the severity of the asthma decreased, the attacks gradually became less frequent and less severe.

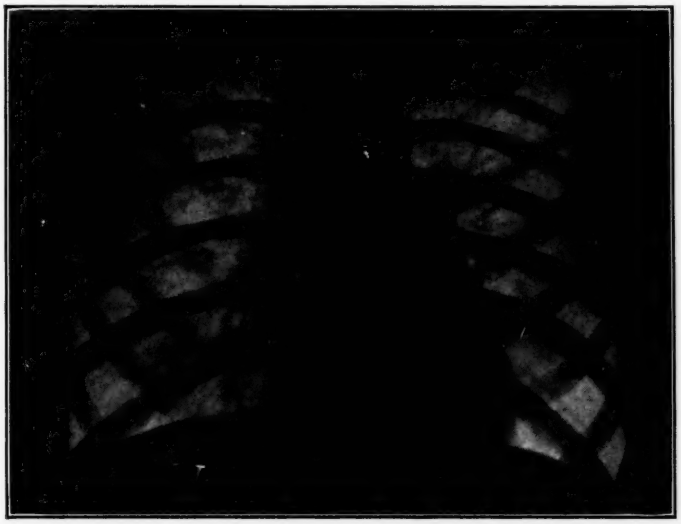

Fig. 2.

Following termination of the treatment, asthma practically disappeared. The liver and spleen were normal once more. At the same time the blood picture improved. On April 15, 1938, the clinical aspect of the patient was normal, with the exception of some small râles over the bases of both lungs. The weight increased from 38.5 kg. to 46 kg., and his general condition was excellent. An x-ray of the lungs taken March 2, 1938, was absolutely identical with previous radiographs.

The leucocyte count did not decline to less than 9,000, and the proportion of eosinophiles not below 25 per cent, which was, according to our experience, an unmistakable sign of insufficient antimony. The clinical cure was only transitory, for on April 20 there were again severe asthmatic attacks increasing in frequency. The liver again enlarged considerably during the subsequent weeks to the level of the umbilicus, and it was moderately sensitive to pressure. The spleen likewise enlarged. The blood cell count increased in total cells and eosinophiles. The course of fuadin, therefore, which we had given in February had had but a transitory effect as was evident from the inadequate reduction of the blood cell count.

TABLE II

WHITE BLOOD CELL COUNTS OF CASE 2 (A. J.)

DATE	LEUCOCYTES	EOSINOPHILES PER CENT	REMARKS
1937			
11/ 2	14,900	64	
11/ 9	15,200	55	11/ 4/37 to 11/22/37 treatment with fuadin (35 c.c.)
11/18	19,400	61	
11/26	16,700	69	
12/ 3	18,500	62	
12/17	7,200	36	12/ 7/37 to 12/22/37 treatment with fuadin (35 c.c.)
12/24	6,900	30	
12/31	10,900	32	
1938			
1/ 7	14,400	28	
1/14	8,500	37	
1/22	8,000	40	
1/28	13,100	39	
2/ 4	13,600	41	
2/14	16,500	37	
2/18	19,700	35	
2/25	17,200	47	
3/ 4	11,300	40	
3/11	14,700	42	
3/18	13,000	47	
4/ 1	11,600	42	
4/15	7,800	27	
4/22	10,200	42	
5/ 6	11,100	50	
5/13	14,100	67	
5/20	14,900	55	
5/27	10,400	36	
6/ 3	11,800	30	
6/10	12,600	64	
6/17	15,300	58	
6/24	11,800	49	
6/30	9,500	34	
7/ 8	11,100	50	
7/15	7,200	32	
7/22	5,800	25	
7/29	4,300	24	
8/ 5	6,100	16	
8/26	6,700	19	
9/23	5,000	19	

In view of the toxicity of antimony, it was impossible to carry out another course of treatment immediately. In the meantime, the asthmatic attacks became more frequent and severe, while the blood picture deteriorated and the spleen further enlarged until it finally extended below the costal margin by the width of three fingers. The general condition obviously became worse by May 20, 1938, and the weight fell to 44.1 kg.

From June 10 to July 29, 1938, another course of antimony was given; this time by means of twenty-five intravenous injections, each of 0.06 gm. tartar emetic dissolved in 10 c.c. of physiologic glucose solution, making a total of 1.47 gm. of tartar emetic.

Ten days subsequent to the onset of the treatment the asthmatic attacks disappeared. The liver was no longer sensitive to pressure and regained its normal size within a month. There was still wheezing with a certain amount of emphysema until the end of July, when it gradually decreased and disappeared completely.

After the treatment had been terminated, the total leucocyte count returned to the normal and the proportion of eosinophiles to between 15 and 20 per cent.

Complete cure has persisted for three months.

Summary.—In view of the absence of eggs of parasites in stools and urine, the bilharzial nature of the disease was accepted from the presence of enlargement of liver and spleen, accompanied by the high eosinophilia, the positive Fairley reaction, and the good therapeutic effect of antimony. Pulmonary involvement was clearly demonstrated by x-ray examination.

The prompt effect of the antimony therapy upon the severe status asthmaticus of the first stage of the disease, as well as the asthmatic attacks during the period of relapse, showed that the bronchial asthma was closely connected with the bilharzia infection. The fact, however, that the x-ray findings of the lungs remained unchanged, contrary to the prompt reaction of the asthma to the therapy, indicated that it was not the anatomic pulmonary changes that gave rise to the asthmatic manifestations.

The blood cell count determined after cure, with its permanently increased proportion of eosinophile (15 to 20 per cent), was in accordance with findings established in similar cases not accompanied by asthma.

CASE 3.—W. A., a merchant, aged 40 years, was the uncle of the patient A. J. (Case 2). His own history before the onset of the present illness and that of his family revealed nothing of importance.

A year and a half previously he had had an attack of dysentery of three to four days' duration. For one year he had suffered from cough with expectoration; asthmatic paroxysms increasing in frequency and severity were also noted. These lasted two to three hours and ended with the expectoration of a glassy sputum. In the course of nine months he lost 27 kg. In May and June, 1937, he was under medical observation for these ailments, during which time enlargement of the liver was symptomatically treated with no success.

The asthma increased until finally the patient was unable to move about freely, so that he underwent treatment in a hospital in Berlin.* There he complained of dyspnea, temporary "asthmalike crises," cough with expectoration, and severe attacks of pain in the upper abdomen. He looked emaciated. Bronchitic râles could be heard all over the emphysematous lungs; the liver extended below the costal arch by a hand's breadth. It was markedly firm and sensitive to pressure, particularly in the vicinity of the gallbladder. The right rectus was rigid. There was no fever. In the urine there were albumin, red blood corpuscles occasionally in large quantities, and from time to time numerous hyaline and granular casts. The blood picture showed 23,000 leucocytes, of which 70 per cent were eosinophiles. The sedimentation rate was normal: 4 to 6 mm. per hour (Linzenmeyer).

The x-ray showed emphysematous lungs with increased striations, especially in both lower fields. The stomach was pushed to the left by the liver which apparently reached the true pelvis.

On July 26, 1937, laparotomy was performed since an hepatic abscess was suspected. The liver was found to be riddled with small, glassy, white nodules the size of a millet seed; two were excised.

*I am greatly indebted to Prof. Dr. Kalk of Berlin for the information about the course of the disease and the findings which were obtained there.

On histologic examination granulation tissue was found, already partly transformed into fibrous tissue, around the pigmented remainder of decayed eggs. It could not be determined whether they were eggs of *S. haematobium* or *S. mansoni*. The granulation tissue showed an immense number of eosinophiles with some giant cells.

On the day following operation some asthma occurred. In the sputum the eggs of *S. haematobium* were detected on one occasion but none could be found in the urine.

The patient received a course of fuadin (50 c.c.) and left the hospital on August 30. On September 20 another course of fuadin (35 c.c.) was started, but this could not be completed. On September 25, 60 per cent of eosinophiles were still present, with a total leucocyte count of 6000.

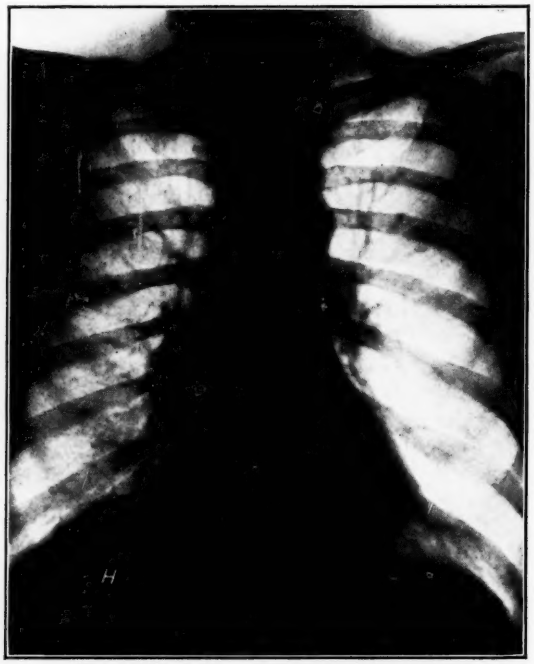

Fig. 3.

When on November 29, 1937, the patient came under our observation, asthmatic breathing was pronounced. The liver was only slightly, if at all, enlarged, but its consistency was increased. The spleen was not palpable. The blood picture showed that the leucocytes increased to 13,200, with 70 per cent eosinophiles. The general condition, however, was satisfactory. The urine was free from pathologic substances and from eggs. In the stools, however, the concentration method revealed the presence of eggs of *S. haematobium*.

The x-ray photograph of the lungs showed the typical multiform picture of bilharziasis associated with emphysema (Fig. 3). The diaphragm was low, the position of the ribs almost horizontal. The striations were markedly increased, radiating from the enlarged and intensified hilum to the superior lobes. Both lungs were riddled by miliary opacities. On the left they were not so close together and were connected with one another by fine threads, giving the appearance of a network, which we have already described. On the right the foci were nearer to

TABLE III

WHITE BLOOD CELL COUNTS OF CASE 3 (W. A.)

DATE	LEUCOCYTES	EOSINOPHILES PER CENT	REMARKS
1937			
7/23	23,000	70	
7/26	23,400	65	
7/28	13,000	27	
8/ 6	13,200	59	
8/ 9	17,000	50	8/ 1/37 to 8/20/37 treatment with fuadin (50 c.c.)
8/11	15,000	55	
8/14	12,000	60	
8/16	12,000	70	
8/18	13,200	65	
8/20	13,400	57	
8/23	12,000	62	
8/25	13,400	70	9/15/37 to 10/ 1/37 treatment with fuadin (35 c.c.)
9/25	6,000	60	
11/30	13,200	70	11/30/37 to 12/15/37 treatment with fuadin (45 c.c.)
12/ 9	18,400	75	
12/16	12,300	73	
1938			
1/10	5,400	42	
1/17	8,500	33	
1/24	10,000	43	
2/10	17,600	70	
2/22	10,800	56	
3/ 1	14,600	73	
3/ 8	9,000	52	
3/15	7,100	63	
3/22	6,600	56	
3/29	5,600	41	
4/ 5	5,200	36	
4/12	5,100	25	
4/19	5,000	26	
4/26	6,700	30	
5/ 3	8,100	25	
5/10	6,100	31	
5/17	5,500	34	
5/24	6,800	31	
5/31	5,500	25	
6/ 7	6,100	26	
6/19	7,300	50	
6/21	6,500	29	
6/28	5,400	52	
7/ 5	5,100	35	
7/12	4,700	26	
7/19	3,900	18	
7/26	5,400	23	
8/ 2	4,800	20	
8/ 9	5,000	18	
8/16	5,000	26	
8/23	7,900	14	
8/30	5,400	25	
9/ 6	5,500	20	
9/13	5,800	18	
9/27	4,200	14	

one another and coalesced, particularly in the inferior lobe. There was thus produced a diffuse cloudy opacity which varied in density in different regions. Farther upward the small foci looked like berries suspended on the dense striations.

From November 30 to December 15, 1937, a course of fuadin was given (45 c.c.). The asthmatic manifestations rapidly abated. From the end of the treatment to

the middle of January, 1938, the clinical condition of the lungs was normal. Similarly, the blood picture showed progressive improvement to the middle of January, although at the beginning there had been 18,400 leucocytes, with 75 per cent eosinophiles. On January 17, 1938, there were 8,500 leucocytes, with 33 per cent eosinophiles. A radiograph taken on that day revealed no changes.

Toward the end of January the blood picture began again to deteriorate and the asthmatic manifestations reappeared. From the beginning of February the patient suffered every evening from severe asthmatic paroxysms which were successfully combated by a mixture of adrenalin-atropine-hypophysin given subcutaneously.

By the middle of February the liver and spleen again enlarged and the pulmonary manifestations further increased. The leucocytes rose to 17,600, with 72 per cent eosinophiles. From February 15 to March 18, 1938, we carried out another (fourth) course of antimony with fuadin (18 injections, 85 c.c.). After the second week of March, no further asthmatic attacks occurred. The liver regained its normal size and the spleen was no longer palpable. The weight increased to 75 kg. The blood picture, from the onset of the treatment to the middle of April, showed progressive improvement, characterized by the decline of the total leucocyte count to normal and the proportion of eosinophiles to about 25 per cent.

The lungs were inspected by x-ray at the beginning of the fourth course of fuadin, at the peak of the asthmatic attacks, and after their disappearance. All pictures were identical with those taken the previous November. There were no further asthmatic attacks. Examinations at intervals of two months to the beginning of June, however, revealed over 20 per cent eosinophiles, which was significant of the fact that complete cure (meaning destruction of all worms) had not yet been achieved. As a matter of fact, from the beginning of June the signs of bronchial asthma reappeared. Both consistency and size of the liver also increased. The spleen, however, did not become palpable. From June 9 to July 29, 1938, therefore, another (fifth) course of antimony was given, this time by means of intravenous injections of 0.06 gm. tartar emetic in 10 c.c. physiologic glucose solution, making a total of 1.71 gm. During the second half of July asthma disappeared. During August the liver regained its normal size and consistency. From the second week of August the eosinophiles attained a level which usually persist for a long time after the bilharzia infection has been cured.

Summary.—The diagnosis of bilharziasis of the liver (*S. haematobium*) was confirmed by histologic examination after laparotomy had been performed. The lungs (x-ray, eggs of parasites in the sputum) as well as the bladder (hematuria) and intestine (detection of eggs) were involved. The blood picture showed a high degree of eosinophilia, and bronchial asthma with most severe paroxysms was noted. The asthma very promptly reacted to antimony therapy, i.e., even after a few injections, which establishes its direct relationship to the schistosoma infection. As shown, however, by x-ray the anatomic pulmonary changes persisted independent of treatment. Thus, it was evident that this type of asthma was not one resulting from pathologic changes of the lungs but one of humoral allergy to the products of the worms and their eggs. Four courses of fuadin had but a transitory effect. It was not before a fifth course of antimony, with tartar emetic, was tried that complete cure was effected.

CASE 4.—P. H., a clerk, aged 42 years, had an interesting family history in that among eight brothers and sisters only one suffered from chronic eczema. His own history was unimportant with regard to the present disease. He had never worked on the land, and as far as he knew he had never come into contact with the water of the Nile or its canals. At no time did he suffer from any trouble with his bladder or intestine. From the beginning of January, 1938, paroxysms of dyspnea with difficult expiration occurred. These had increased in frequency to several times a day. They persisted for a half to one hour, often longer, and resulted in heavy cough. In the intervals, respiration was more or less difficult, and there was cough with expectoration of mucus.

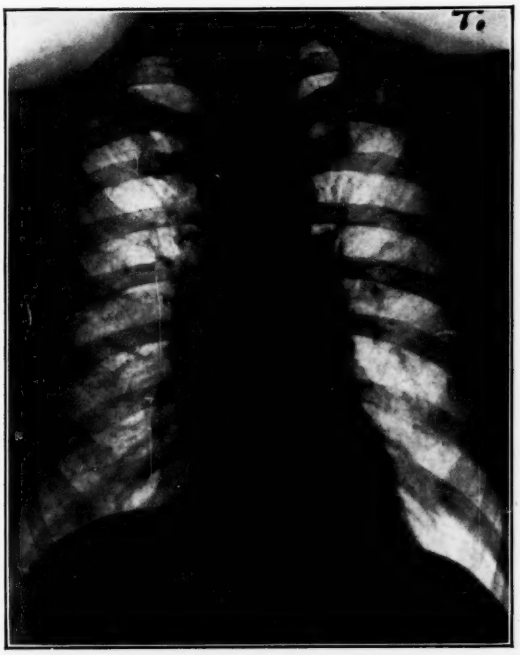

Fig. 4.

On admission, the patient was having a paroxysm of severe asthma. The lungs were extremely emphysematous. The liver was not enlarged, and the spleen just palpable. During the first three weeks the temperature remained between 37.6° and 38° C. rectally. The urine was free from pathologic substances, but there was marked nycturia, the amount of urine passed during the night being about twice that passed in the day. Masses of eosinophiles were detected in the sputum. Three examinations revealed no evidence of parasitic eggs either in the sputum or in urine or stools. The sedimentation rate of the red blood corpuscles was within normal limits, in spite of the rise of temperature: 9 mm. per hour (Linzenmeyer). There was a leucocytosis of 19,500, with a marked increase of eosinophiles (40 per cent).

The x-rays of the lungs (May 4, 1938) showed markedly increased striations in both pulmonary fields, particularly in the right inferior lobe. The striations partly formed a network, especially in the left superior lobe, the knots of which were represented by soft foci the size of a pea. Such foci were also found in both inferior lobes and were, on occasion, confluent with the adjacent foci, thus

forming shadows the size of a bean. The hilum was enlarged and intensified on both sides, particularly on the right. The intradermal bilharzia reaction was markedly positive.

The x-ray appearance of the lungs characteristic of pulmonary bilharziasis, the typical blood findings, and the positive result of the Fairley reaction established the diagnosis of pulmonary bilharziasis in spite of the absence of parasitic eggs. Accordingly, the type of bronchial asthma we were considering here was probably bilharzial in origin which was demonstrated by the result of the specific therapy. We gave fuadin from May 5 to June 2, 1938. The patient received sixteen injections containing a total of 75 c.c. fuadin solution.

As early as one week after the commencement of the treatment no further asthmatic paroxysms occurred. In four weeks the emphysema as well as wheezing disappeared, and the temperature dropped to normal. The total leucocytes dropped to subnormal values and the eosinophiles to 8 per cent. There was no transitory reactive increase of eosinophiles, as usually happens at the beginning of specific treatment. Nevertheless, the radiograph taken on June 21, 1938, did not show any changes compared with that of May 5, except lessened emphysema, nor did the radiograph taken on September 20, 1938. Toward the end of August the patient was looked upon as cured with regard to clinical findings as well as blood picture.

About the middle of September, however, there was a recurrence of some wheezing, although the condition of the blood remained good and respiration was subjectively normal.

From September 23, 1938, a second course of antimony was given; this time intravenous injections with 0.06 gm. tartar emetic, dissolved in 10 c.c. of physiologic glucose solution, were used.

TABLE IV

WHITE BLOOD CELL COUNTS OF CASE 4 (P. B.)

DATE	LEUCOCYTES	EOSINOPHILES PER CENT	REMARKS
1938			
5/ 3	19,400	40	
5/ 8	14,800	33	
5/10	11,000	39	
5/13	8,300	60	
5/17	12,600	41	
5/20	7,100	43	
5/23	9,700	54	
5/27	9,900	26	
5/31	7,100	33	
6/ 3	7,600	23	
6/ 7	8,000	23	
6/11	6,000	17	
6/15	5,700	17	
6/18	6,200	20	
6/21	7,900	12	
6/24	7,100	15	
6/28	5,600	15	
7/ 5	6,000	11	
7/ 1	6,500	21	
7/12	6,800	15	
7/18	6,300	18	
7/25	7,200	13	
8/ 1	5,200	8	
8/16	5,700	20	
8/22	7,700	5	
9/ 2	5,500	12	
9/20	3,500	8	
9/29	3,200	6	

Summary.—A case of severe typical bronchial asthma showed the following remarkable points: (1) leucocytosis and high eosinophilia; (2) focal infiltrations of the lungs and increased striations, (3) permanent rise in temperature to about 38° C., and, (4) positive intradermal reaction for bilharziasis.

In view of these facts we were able definitely to diagnose bilharzia infection with pulmonary involvement in spite of the fact that there was no proof of infection (which is the rule). Antimony treatment caused the disappearance of the asthmatic paroxysms in a very short time, which made it evident that there was a causal relationship between asthmatic manifestations and bilharzia infection. The pathologic x-ray appearance of the lungs, however, remained unchanged during the successful treatment. Thus, it became obvious that the bronchial asthma was not induced by the anatomic pulmonary changes.

DISCUSSION

Before attempting to determine the nature of bilharzial asthma we should discuss the symptoms of pulmonary bilharziasis, i.e., the pulmonary involvement during the course of bilharzia infection. It is only by such knowledge that one can differentiate between pulmonary bilharziasis and bilharzial asthma.

The fact that the parasites of bilharziasis of the bladder and intestine, *S. haematobium* and *S. mansoni,* are able to induce the formation of pulmonary foci, which, as a rule, they do, has always been known to pathologic anatomists (Belleli,[9] Turner[10]). Recently, Shaw and Ghareeb[11] presented a most detailed study of this subject. In the vast majority of cases these foci remain latent clinically, and in others their clinical manifestations appear to be complications of a typically localized schistosoma infection. During the incubation period of tertian bilharziasis of bladder or intestine, i.e., in the period between the penetration of the larvae into the skin and the settling of the worms in the venous system of the bladder or rectum, *transitory* clinical symptoms in the lungs, as bronchitis and bronchopneumonia, are not rare and apparently more frequent in Europeans than in natives. The pulmonary manifestations of the incubation period, which Lawton and Fairley were the first to describe, can be easily understood from the development of the parasite and the stages of its migration. From this one must separate tertian isolated pulmonary bilharziasis, in which as a rule, the typical localization of the schistosoma infection with involvement of bladder or intestine is absent. The liver and spleen, however, are mostly affected. Physical findings in the lungs are usually insignificant. Contrary to this, x-ray inspection reveals an extensive process, as seen in the cases described. Pulmonary tuberculosis is often suspected. In the blood, however, without exception, a leucocytosis is en-

countered (up to 70,000), which is almost exclusively due to the increase in the number of mature eosinophiles, the proportion of which may rise to 70 to 80 per cent. In contrast to this we usually find only moderate eosinophilia (5 to 15 per cent) in cases of typically localized bilharziasis of bladder and intestine and a normal leucocyte count. The specific skin reaction for bilharziasis is positive. When treated with antimony, which is a specific therapeutic drug, the general manifestations of the disease disappear even after a few injections. At the beginning of the treatment the blood picture shows an increase in the number of leucocytes and eosinophiles, followed by a gradual fall. Nevertheless, even if complete cure has been attained, the number of eosinophiles remains at about 15 per cent for months or years. While liver and spleen quickly regain their normal size under specific treatment, the pulmonary involvement, as a rule, shows no retrogression, as proved by the x-ray. On the whole, the pulmonary type of schistosomiasis is more resistant to therapy than other typical localizations of this disease.

If bronchial asthma in schistosoma infection were a consequence of the anatomic pulmonary process, as has been assumed by Suarez,[1] it should regularly accompany bilharziasis of the lungs. It is, however, a rare complication.

It appears evident, therefore, that bilharzial asthma is an allergic reaction to the products of the worms or their eggs.

The following observations speak in favor of this thesis: (1) The existence of a high eosinophilia and of an antibody in the blood, as proved by the Fairley reaction. (2) In one patient the asthmatic attacks occurred simultaneously with urticaria; in this case the lungs proved to be healthy roentgenologically. (3) The disappearance of asthma coincident with specific antimony treatment, despite the persistence of anatomic lesions in the lungs.

It is comprehensible that this type of allergic asthma is not found in patients who suffer from bilharziasis of bladder or intestine. These are merely local processes. There is no direct influence upon the systemic condition. In chronic pulmonary bilharziasis, however, the products of metabolism of the parasites flood the organism.

SUMMARY

1. Based upon six observations, four of which have been our own patients, the picture of bilharzial asthma is here discussed.

2. It is a type of allergic bronchial asthma occurring only in the generalized type of the disease.

3. Improvement of asthma is coincident with specific treatment of the disease.

4. Asthma is not due to anatomic changes in the lungs, since these persist long after the asthma has disappeared. Pulmonary lesions are common, whereas asthma is rare.

5. With bilharzial asthma there are leucocytosis and high degree of eosinophilia.

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THE ROLE OF ALLERGY IN BRONCHIECTASIS*

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THIS presentation is the continuation of a study of bronchiectasis from an allergic standpoint given in a preliminary report[1] more than a year ago. At that time the opinion was expressed that allergy was the etiologic background for bronchiectasis and its frequently associated sinusitis. Further observation has strengthened this opinion.

Sufferers from sinusitis and bronchiectasis frequently seek relief in a change of climate. The close association of these conditions has been common knowledge for many years, yet there has been no universally accepted explanation of it. Most patients with sinusitis coming to our locality have never had cytologic examinations of nasal secretion, nor any other allergic study, for nose and throat specialists are generally remiss in differentiating cases having an allergic background. Sinusitis is a common complication of nasal allergy, and the two conditions are frequently associated. Hansel[2] observed that approximately 44 per cent of patients with nasal complaints are allergic. We began routine cytologic examinations of bronchiectatic sputum because these cases so frequently have sinusitis or allergic rhinitis. It was found that such sputum, if it was repeatedly examined, so commonly had an increased per cent of eosinophiles that we began investigating these cases from other allergic aspects. Incidentally, the most purulent bronchiectatic sputum may contain more than 50 per cent of eosinophilic leucocytes. It has been our observation that a high percentage of patients suffering from bronchiectasis have clinical allergy or abnormal bronchial or nasal eosinophiles; they usually have both of these conditions. This observation has made us feel that a common basis of allergy explains the association of bronchiectasis and sinusitis.

Skin testing performed both with scratch and intracutaneous methods in bronchiectasis revealed that the large majority gave positive reactions. We have found that some patients were negative even though high percentages of eosinophiles were found in the nasal and bronchial secretions, and, therefore, true atopy could not be demonstrated. However, this is also observed in other allergic conditions.

Because of this observation of the association of allergy and bronchiectasis, we proposed in an earlier article[1] that an allergic type of bronchiectasis be included in the classification of this disease.

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*From the Tucson Clinic.

Read before the Annual Meeting of the Association for the Study of Allergy, San Francisco, Calif., June, 1938.

TABLE I

8 CASES OF BASAL ALLERGIC BRONCHITIS WITH CLINICAL DIAGNOSIS OF BRONCHIECTASIS

CASE	NAME	DIAGNOSIS OF BRONCHIECTASIS		SINUSITIS	ASTHMA	NASAL ALLERGY	EOSINOPHILE PER CENT		SKIN SENSITIZATION	REMARKS AND TREATMENT RESULTS
		LIPIODOL X-RAY	CLINICAL				NASAL	SPUTUM		
1	D. H.	0	+	+	Mild with colds +	V.M.R. +	None to examine		Pollens Inhalants +	Shadow along left descending bronchial trunk Not treated
2	E. H.	0	+	++	+	0	10	0	Foods Molds +	Little improvement by treatment
3	C. Y.	0	+	0	0	0	–	0	Pollens Foods Inhalants +	Marked improvement by treatment; relapse without
4	E. S.	0	+	+	0	V.M.R. +	0 10	0 5	Pollens Foods Inhalants +	Relieved all lung symptoms by treatment
5	J. M.	0	+	+	+	H.F. +	–	–	Pollens Foods Inhalants +	Relieved of symptoms by treatment
6	F. G.	0	+	+	+	V.M.R. +	75	–	Pollens Foods Inhalants +	Moderately improved sputum 50 per cent reduced by treatment
7	R. H.	0	+	++	0	0	0	–	Pollens Foods Inhalants +	Marked improvement. Relieved all sputum by treatment
8	A. G.	0	+	+	+	H.F. V.M.R. +	–	50	Pollens Foods Inhalants +	Marked improvement. 30 c.c. sputum relieved by treatment

In studying bronchiectasis by means of lipiodol x-rays, cytologic examination of sputum and nasal secretion, by taking a searching history for allergic manifestations and skin testing, we have found a few cases which presented all the clinical features of a marked bronchiectasis, except bronchial dilatation, as revealed by lipiodol x-rays. These cases often had a duration of ten years or more, raised daily more than 30 c.c. of purulent sputum, and had coarse basal râles. We chose, therefore, to make a diagnosis of basal allergic bronchitis. This term is used to indicate that allergic bronchitis, at least from a clinical standpoint, predominates at the base of the lungs. These cases were referred to us with a diagnosis of bronchiectasis, and we concurred in this diagnosis until it was disproved by lipiodol x-rays.

We observed all stages from basal allergic bronchitis and mild bronchiectasis to moderate and far-advanced bronchiectasis in patients, and noted that the majority had strong evidence of allergy. This suggested that allergy was the primary background of bronchiectasis. Usually bronchiectasis is associated with a chronic low-grade type of allergy. Incidentally, in our series of bronchiectasis patients, lipiodol x-rays very frequently revealed occluded bronchioles terminating abruptly, as well as narrowed caliber of the small bronchial branches. Both of these conditions are frequently found in lipiodol x-rays of cases of asthma.

The results of treatment have been, as one might imagine, in proportion to the advancement of the disease. In cases of basal allergic bronchitis, the results are usually good. In slight and moderate bronchiectasis, symptoms are commonly relieved or markedly benefited. Frequently, even far-advanced cases are improved in that the cough and purulent sputum are markedly reduced. However, lipiodol x-rays seldom reveal any retrogression of bronchiectatic dilatation. We have obtained marked benefit in many cases whose improvement was at a standstill in our locality.

EXPLANATION OF DATA IN TABLES

In order to avoid making any selection of cases we have included some patients about whom our information is incomplete. However, with the exception of one patient who had a typical history and findings, only cases having lipiodol x-ray bronchiectasis have been used.

In this tabulation of data skin sensitization was determined by the scratch and intradermal methods, the latter performed if little or no reaction resulted with the scratch test.

True bronchial asthma has been carefully distinguished from cardiac asthma, the dyspnea of pulmonary emphysema (often relieved by epinephrine), and the rather constant wheezing of patients with chronic bronchitis or bronchial obstruction. The caption "Asthma" means an undoubted history of it or an attack of asthma while under our care. Also the caption "Hay Fever" designates a clear history of active pol-

linosis corresponding to the pollinating season of hay fever weeds or grasses, or its occurrence while under our observation.

The diagnosis of nasal allergy was made on the history and observation of the case, often aided by the rather typical appearance of the nasal mucosa. Polyposis, hay fever, and vasomotor rhinitis (V.M.R.) are placed under the caption "Nasal Allergy." Under the caption "Sinusitis" the presence or absence of this condition is indicated after a careful examination had been made by an otolaryngologist. The degree of sinusitis is indicated by plus signs—one to three. The percentage of eosinophiles is usually indicated in round numbers of five. This is intended only to be approximate for, since mucus cannot be spread on a slide evenly or thinly like blood, accurate determination cannot be made. The extent of bronchiectasis is indicated by plus signs, one meaning minimal; two, moderately advanced; three, far advanced. Usually transverse and anteroposterior stereoscopic films were taken as a routine procedure. Pollens are distinguished from other inhalants for clarity. The term "polyp" always means mucous polyp.

Under the caption "Remarks and Treatment Results," treatment means allergic management and results of treatment refer specifically to bronchiectasis.

ANALYSIS OF DATA

As regards the following estimation of percentages: the examinations indicated by a question mark or no examination, indicated by a dash, are considered negative.

Of 46 cases of bronchiectasis, 31, or 67.3 per cent, had definite sinusitis; skin sensitization was positive in 38, or 82.6 per cent; hay fever, polyps, or nasal allergy was present in 27, or 58.1 per cent; including sinusitis with hay fever, nasal polyps, and nasal allergy, the percentage of nasal involvement was 82.6 per cent. Asthma was present or a history of it was given in 15, or 32.6 per cent. Abnormal eosinophile percentage (10 per cent or more) occurred in the nasal or bronchial secretion in 33, or 71.7 per cent, even including many inadequate and incomplete examinations. Presumably this percentage would have been higher if more examinations had been made. We do not consider that improvement following allergic management indicates the presence of allergy, although it is suggestive of allergy in patients whose previous condition has been stationary. Also, marked increase of sputum following the ingestion of certain foods, or coincident with the season of pollination of weeds causing hay fever, is not regarded as evidence of allergy without other manifestations of hypersensitivity. Aggravation of sputum-raising by desensitization therapy likewise is not regarded as evidence of allergy, although it is quite suggestive of it.

According to one's criteria for allergy, these data can be interpreted in various ways. We have considered that asthma, hay fever, vasomotor

TABLE II

46 CASES OF BRONCHIECTASIS

CASE	NAME	DIAGNOSIS OF BRONCHIECTASIS		SINUSITIS	ASTHMA	NASAL ALLERGY	EOSINOPHILE PER CENT		SKIN SENSITIZATION	REMARKS AND TREATMENT RESULTS
		LIPIODOL X-RAY	CLINICAL				NASAL	SPUTUM		
1	W. V.	++	+	++	+	H.F. +	–	30	Inhalants +	Moderately improved by treatment
2	R. C.	+++	+	0	0	0	20	5	Inhalants Pollens Foods +	Not treated
3	M. R.	+++	+	+++	0	H.F. +	–	–	Pollens Inhalants +	Severe sinusitis and nasal allergy, Bermuda hay fever and asthma Little treatment
4	F. L.	++	+	++	+	0	–	20	Molds Foods +	Not treated
5	V. I.	+++	+	+	0	0	–	0 20 10	Foods Pollens Inhalants +	Observed for 10 years Marked scratch food reactions Not treated
6	W. Z.	++	0	+	+	H.F. +	–	50	–	Not treated
7	R. F.	+++	+	++	0	H.F. Polyps +	50	25	Pollens Inhalants +	Olive tree hay fever moderately improved by treatment
8	G. S.	+	0	0	0	V.M.R. +	–	20	Scratch only 0	Not treated
9	R. S.	++	0	+	+	0	–	–	Pollens Inhalants +	Unimproved by treatment

H. F.=Hay fever.
V. M. R.=Vasomotor rhinitis.

TABLE II—Cont'd

10	M. S.	++	+	++	+	0	–	12	–	Atopic dermatitis all of life 12 attacks pneumonia not treated
11	A. M.	++	+	++	0	Polyps +	0 26 3	0 60 26 3 5	Pollens +	Marked improvement by treatment Relief at high altitudes
12	F. S.	++	0	++	+	V.M.R. Polyps +	10	5 15	Repeated intradermal 0	Not improved by treatment Severe cough and nasal allergy; daily asthma
13	L. B.	++	+	+++	0	0	–	20	Pollens Inhalants +	Sputum 75 per cent reduced by treatment; lobectomy previously advised
14	E. W.	+++	+	+	0	0	0 0	0 0	Foods Molds +	No improvement by treatment
15	D. W.	+++	+	0	0	0	–	10	Inhalants +	Moderately improved by treatment
16	H. F.	+++	+	0	0	H.F. +	10	10	Pollens Inhalants Foods +	Not treated
17	P. F.	+++	+	++	0	0	–	–	Pollens Inhalants +	Treated No benefit
18	D. W.	Bronchoscope confirmed +	+	0	0	0	30	0	Pollens Foods Inhalants +	Bronchiectasis diagnosed before developed lung abscess Not treated
19	C. G.	++	Bronchoscope confirmed +	+	+	H.F. +	60	40	Inhalants Foods +	Pulmonary tuberculosis cured by thoracoplasty Negative sputum persisted Not treated

TABLE II—Cont'd

CASE	NAME	DIAGNOSIS OF BRONCHIECTASIS		SINUSITIS	ASTHMA	NASAL ALLERGY	EOSINOPHILE PER CENT		SKIN SENSITIZATION	REMARKS AND TREATMENT RESULTS
		LIPIODOL X-RAY	CLINICAL				NASAL	SPUTUM		
20	N. C.	+++	Broncho-scope confirmed +	++	+	V.M.R. +	0 0	12	Foods Inhalants +	Desensitization treatment aggravated and discontinued
21	C. A.	+++	+	0	0	H.F. +	–	20	Pollens +	Desensitization treatment aggravated and discontinued
22	R. M.	+++	+	0	+	H.F. +	–	–	Inhalants Pollens +	Unimproved by treatment
23	B. R.	++	+	+	+	H.F. +	–	20	Pollens Inhalants +	Foods aggravate sputum Moderately improved by treatment
24	E. N.	++	+	+	+	Polyps +	–	10	Foods Inhalants +	Severe atopic dermatitis Foods aggravate sputum Not treated
25	M. F.	++	+	+	+	0	0	10	Pollens Foods Inhalants Molds +	No benefit Arizona 3 months Entire relief of sputum by treatment
26	R. T.	+	+	++	+	V.M.R. H.F. +	10	10	Pollens Inhalants Foods +	Arizona benefited sinusitis but not bronchiectasis Not treated
27	F. S.	+	0	+	0	V.M.R. +	15	1	Inhalants +	Right basal fibrous pleuritis Markedly improved by treatment

TABLE II—Cont'd

28	H. J.	+++	+	+++	+	Polyps +	–	30	Pollens Foods Inhalants +	Severe saccular bronchiectasis Foods aggravate Not treated
29	C. M.	++	+	0	0	V.M.R. Polyps +	–	15	Pollens Foods Inhalants +	Sputum formerly 75 c.c. 80 per cent reduced by treatment
30	T. M.	++	+	0	0	0	–	10 0 10	Scratch only 0	Not treated
31	S. R.	+++	+	+	0	V.M.R. +	40	5 9 15	Foods Inhalants +	Severe saccular bronchiectasis 35 years' duration Not treated
32	P. S.	++	+	+	0	V.M.R. +	5	20	Foods Inhalants +	Not treated
33	C. W.	–	+	0	0	V.M.R. H.F. Polyps +	–	50	–	Severe nasal allergy and polyps Not treated
34	P. M.	+++	+	0	0	0	–	–	–	Symptom free 4 years Lipiodol x-ray same Marked improvement by treatment
35	H. W.	++	+	+	0	0	–	0	Foods Inhalants +	Not treated
36	S. W.	+++	+	0	0	0	0 15	–	Pollens Inhalants +	18 years' duration Suptum and cough; marked improvement by treatment
37	H. B.	+++	+	+++	0	0	–	2 12	Pollens Foods Inhalants +	5 attacks pneumonia Benefit food elimination Not treated

TABLE II—CONT'D

CASE	NAME	DIAGNOSIS OF BRONCHIECTASIS		SINUSITIS	ASTHMA	NASAL ALLERGY	EOSINOPHILE PER CENT		SKIN SENSITIZATION	REMARKS AND TREATMENT RESULTS
		LIPIODOL X-RAY	CLINICAL				NASAL	SPUTUM		
38	R. S.	++	+	+	0	H.F. V.M.R. +	–	 5	Pollens Foods Inhalants +	Moderately improved
39	E. G.	+	0	0	?	V.M.R. Polyps +	–	0 0 40	 Foods Inhalants +	Pulmonary emphysema Not treated
40	L. K.	+++	+	++	0	0	5	5 0 10	Foods Inhalants +	Left lobectomy not successful Not treated
41	G. H.	+++	+	+	0	H.F. +	–	–	Pollens +	Relieved by pneumothorax elsewhere
42	W. C.	++	+	?	+	0	–	–	Pollens Inhalants +	Just started treatment
43	E. S.	+	+	?	0	0	5	40	Pollens Foods Inhalants +	Not treated
44	V. C.	+++	+	+	0	0	10 0	0 20	Pollens Foods Inhalants +	Aggravated by pollens Marked improvement by treatment
45	J. H.	++	+	+	0	V.M.R. +	–	5 5 2	Molds Foods Inhalants +	Entire relief two occasions at coast climate Not treated
46	S. B.	++	+	+	0	Polyps +	10	0	Foods Inhalants +	Moderately improved by treatment

rhinitis, mucous polyps, or atopic dermatitis are definite evidence of allergy. If one considers that 10 per cent or more of eosinophilic leucocytes in the nasal or bronchial secretion are an indication of the presence of allergy even without other supporting data, then approximately 90 per cent of patients (actually 89.1 per cent) suffering from bronchiectasis have clinical allergy or abnormal eosinophile percentages in nasal or bronchial secretions. If, for instance, it is considered that 25 per cent or more of eosinophiles in nasal or bronchial secretion, together with other manifestations, indicate allergy, then this percentage is 69.5 per cent. In the above estimation of percentages, skin sensitivity has been ignored entirely. It should be remembered in this connection that frank hay fever or asthma frequently does not constantly exhibit nasal or bronchial eosinophiles in abnormal amounts. Speaking conservatively, evidence of allergy in bronchiectasis is strikingly higher than in an average group of normal individuals.

As regards treatment of these cases of bronchiectasis, we have utilized the usual allergic methods, including elimination of allergens from the environment; desensitization therapy; air-filtered rooms; elimination diets; and other measures as indicated. Nineteen patients were given sufficient treatment to evaluate results. Of these 19, 8 were markedly benefited; 6 were moderately benefited; and 5 were unimproved. Treatment of 7 basal allergic bronchitis patients resulted in one moderately improved, 5 markedly benefited, and one unimproved.

SUMMARY

1. A study of a series of 46 cases of bronchiectasis from an allergic standpoint reveals that a high percentage was found to have definite evidence of allergy based on the presence of hay fever, asthma, nasal polyps, atopic dermatitis, and abnormal amounts of eosinophiles in nasal or bronchial secretions, excluding skin tests entirely.

2. Bronchiectasis can be closely simulated by basal allergic bronchitis, the only distinguishing evidence being lipiodol x-ray examination.

3. Bronchiectasis in the majority of patients can be favorably influenced by allergic management.

4. The common association of sinusitis and bronchiectasis can be explained on the basis of allergy.

REFERENCES

1. Watson, S. H., and Kibler, C. S.: A New Conception of Bronchiectasis, Southwestern Med. **21:** 428, 1937.
2. Hansel, F. K.: Allergy of the Nose and Paranasal Sinuses, St. Louis, 1936, C. V. Mosby Co.

TABLE II—CONT'D

CASE	NAME	DIAGNOSIS OF BRONCHIECTASIS		SINUSITIS	ASTHMA	NASAL ALLERGY	EOSINOPHILE PER CENT		SKIN SENSITIZATION	REMARKS AND TREATMENT RESULTS
		LIPIODOL X-RAY	CLINICAL				NASAL	SPUTUM		
38	R. S.	++	+	+	0	H.F. V.M.R. +	–	5	Pollens Foods Inhalants +	Moderately improved
39	E. G.	+	0	0	?	V.M.R. Polyps +	–	0 0 40	Foods Inhalants +	Pulmonary emphysema Not treated
40	L. K.	+++	+	++	0	0	5	5 0 10	Foods Inhalants +	Left lobectomy not successful Not treated
41	G. H.	+++	+	+	0	H.F. +	–	–	Pollens +	Relieved by pneumothorax elsewhere
42	W. C.	++	+	?	+	0	–	–	Pollens Inhalants +	Just started treatment
43	E. S.	+	+	?	0	0	5	40	Pollens Foods Inhalants +	Not treated
44	V. C.	+++	+	+	0	0	10 0	0 20	Pollens Foods Inhalants +	Aggravated by pollens Marked improvement by treatment
45	J. H.	++	+	+	0	V.M.R. +	–	5 5 2	Molds Foods Inhalants +	Entire relief two occasions at coast climate Not treated
46	S. B.	++	+	+	0	Polyps +	10	0	Foods Inhalants +	Moderately improved by treatment

rhinitis, mucous polyps, or atopic dermatitis are definite evidence of allergy. If one considers that 10 per cent or more of eosinophilic leucocytes in the nasal or bronchial secretion are an indication of the presence of allergy even without other supporting data, then approximately 90 per cent of patients (actually 89.1 per cent) suffering from bronchiectasis have clinical allergy or abnormal eosinophile percentages in nasal or bronchial secretions. If, for instance, it is considered that 25 per cent or more of eosinophiles in nasal or bronchial secretion, together with other manifestations, indicate allergy, then this percentage is 69.5 per cent. In the above estimation of percentages, skin sensitivity has been ignored entirely. It should be remembered in this connection that frank hay fever or asthma frequently does not constantly exhibit nasal or bronchial eosinophiles in abnormal amounts. Speaking conservatively, evidence of allergy in bronchiectasis is strikingly higher than in an average group of normal individuals.

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DISCUSSION

DR. HARRY L. ALEXANDER, St. Louis.—I read this paper with a great deal of interest and it was new to me because I had not read the previous communication by these authors to the effect that allergy plays such a very important role in bronchiectasis. I was very much surprised to learn that their statistics indicated that over 90 per cent of cases of bronchiectasis had an allergic background. I thought this very surprising, and, as a matter of fact, I thought it was so surprising that I took the trouble to break down these statistics.

I did not quite agree on the evidence of some of these cases that they were allergic, but, having analyzed them with great care, I came to the same conclusion as the authors: that unquestionably, from the data presented, a great majority do have an allergic background. This may be a matter of some importance because the inference of etiology of the disease must come in.

In so far as treatment is concerned, it is stated, naturally, that the worse the bronchiectasis is, the less effective the treatment. I was interested to consider the correlation of the degree of improvement in the cases with the degree of allergy. It appears that the less the indication of allergy, the better the treatment, and that in the cases that were most allergic or had most evidence of allergy, the less successful was the treatment. This is quite obvious if one takes the trouble to analyze the tables in this way. The answer may be, the less allergy, the easier the allergy is to treat. The question comes up, however, if there is very little allergy and, in some cases, doubtful allergy, the ratio of allergy to bronchiectasis must be less in these particular instances.

This point needs clarification. I make it with reservation because it is not fair to break down statistics and select certain elements to make a point of them; and, secondly, it is not fair to criticize a case when one has not seen the patient; I bring it up in order to ask Dr. Kibler to reconcile this point. This paper will be scrutinized by many interested in thoracic disease, and they may then treat their patients from an allergic approach. It may be better to interpret the paper for them rather than have them find that in patients obviously very allergic, treatment is not so successful.

There is one point—it is a minor one—that needs discussion and that is a new term, namely, "basal allergic bronchitis." These patients have so much mucus which comes from their mucous glands, and we know from autopsy observation that the mucous glands are greatly hypertrophied and are not at the base of the lung; but are greatest at about the 5 mm. or 4 or 3 mm. bronchioles, below which they disappear.

DR. E. WOOD PHILLIPS, Phoenix, Ariz.—Being a neighbor of Doctors Watson and Kibler, I have had the privilege of knowing about this work for some time and have seen some of their clinical material. Perhaps it ought to be emphasized that many of their bronchiectatic cases have come to them, not for allergy, but for treatment in their chest clinic; and that some of these patients to whom they have given a considerable amount of relief by the application of accepted methods of allergic investigation, are not the chronic asthmatics with productive cough and sinus disease. They are the sort who come in for differentiation from tuberculosis, because they do spit blood and have copious sputum, their general condition is poor, and they have lost weight.

I have been able by the same method in a smaller number of cases, too small to be of value statistically, in various instances to get similar favorable results in bronchiectatics that would otherwise be unrelieved.

I do not give lipiodol any more to asthmatics. The patients that I had good results with were the ones that responded to the inversion test, and when inverted posturally, drained quite a lot of purulent sputum. In those I saw of my own, the percentage of eosinophiles in their sputum, in the favorable cases, ran anywhere from 15 to 65 per cent.

I would like to ask Dr. Kibler if he has had any trouble in getting rid of the lipiodol that was instilled into the bronchi of the asthmatic patients. This treatment for the relief of asthma has become popularized, and we see from year to year an increasing number of patients who get lipiodol in the bronchi and cannot get it out. I recall seeing two patients during the current year; one of them had had lipiodol in his bronchial dilatations in the base for two years and two months from the time it was instilled. His condition grew steadily worse and he died.

Recently, I saw in consultation a woman with a bad case of asthma who had been able to be up and about, taking quite a lot of adrenalin, but did not require hospitalization. To make sure whether or not she had bronchiectasis, she was given iodized oil. Her asthma became steadily worse, practically a status asthmaticus. She was inverted and attempts were made to aspirate the stuff bronchoscopically, without success. She has had helium and oxygen, with no benefit. I wonder if the doctor will tell us whether he has had similar misfortunes.

DR. FRED FIRESTONE, San Francisco.—I am quite in agreement with Dr. Alexander in the problem of not coining a new term of "basal allergy." Some of the cases described by Dr. Watson here would very well fit into our old classification of chronic nontubercular bronchopneumonia.

As to the incidence of allergy, I should like to ask Dr. Watson the incidence of primary bronchiectasis in a person who is nonallergic and who does not show upper respiratory system infection such as he described, with polyposis and sinusitis.

Our experience has been that we see many people with basal chest râles and in the final interpretation, including the bronchoscope and lipiodol instilled directly, we have not been able to pick up characteristic bronchiectatic cavities, whereas clinically you would certainly expect to find them.

Merely the presentation of an enlarged dilated bronchus has not been a characteristic finding that we emphasize in bronchiectatic conditions. We feel that one must have definite cavitation with stagnation and pooling of lipiodol to make a clinical diagnosis of bronchiectasis.

Some of these cases described by the doctor, certainly those with a temperature rise, indicate that there was definite stagnation in the bronchiectatic cavity and a secondary infection was present, and until the secondary infection cleared up, that is, the acute paroxysm of fever, I am quite sure that the doctor did not attempt to treat the underlying allergy.

DR. KIBLER.—I realize this series of cases is rather small and I do not think we can form any very far-reaching conclusion on the question of the greater the allergy, the less successful the treatment. Our impression is that there is always a very low grade, or usually a very low grade,

type of allergy present in most of these cases; that is, they do not have, usually, acute asthma, or acute allergic nose that is stopped up and obstructed, but they have more chronic symptoms. It seems to me that question has to be decided by a good deal more work than we have done here at the present time.

So far as Dr. Phillips' question is concerned, practically all of these cases have come to us not for allergy at all but for the treatment of a chronic cough and sputum-raising. A few we have picked up because they have consulted us for allergy, but this percentage is quite low. Certainly there is trouble at times in getting rid of lipiodol. We see it persist in x-ray films for many months and even longer, but we have not encountered any difficulty at all in raising the lipiodol after it is used for diagnostic purposes. I do not think it is entirely harmless.

As to Dr. Firestone's question and Dr. Alexander's as well, concerning the objection to the term "basal allergic bronchitis," we have used that term on the few cases that we found, mainly because we and the doctors referring these cases had been mistaken in making a diagnosis of bronchiectasis. They had definite basal râles and a large amount of sputum over a duration of ten years or more. Often their symptoms apparently were more in the base of the lungs than elsewhere. This group of cases, which was only 6, were all shown to be very allergic and, incidentally, this group had much more asthma than the other group. Usually their diagnosis was asthma and bronchiectasis.

Special Reports

PINE POLLEN ALLERGY

ALBERT H. ROWE, M.D.
OAKLAND, CALIF.

PINE pollen allergy has not been recorded in the literature previously. Its occurrence, therefore, in one patient who gave large skin reactions by the scratch method to the pollens of various species of pine, and whose asthma was controlled largely through hyposensitization with specific pine pollen extracts has prompted this report. Several other patients living in the pine belt of California have given two- to four-plus reactions with intradermal tests with various pine pollen extracts. A physician, moreover, told me of the control of nasal and bronchial allergy in his wife with hyposensitization to an extract of *Pinus murrayana* (tamarack pine) pollen to which reactions occurred. These experiences indicate that pine pollen allergy occurs possibly more frequently than may be suspected in patients living in pine-covered areas in the world and here in California in the 700 mile stretch of the western and eastern slopes of the Sierra Nevada mountains where many species of pines are abundant.*

CASE REPORT

A man of 37 years developed asthma fourteen years ago in Sonoma County. Since then symptoms have recurred every year starting in February and continuing until late fall, being especially severe from June to September. Moderate hay fever only occurred thirteen and fourteen years ago. Since childhood he has had an itching, papular, and lichenified dermatitis on the dorsum of both hands and asthma has been present. Although he had lived in Sonoma County until thirteen years ago, since then he has been in the Tahoe region of the Sierras from February to December of each year, in the pine tree belt. The family history was negative except for asthma in one sister. Physical examination was negative except for moderate emphysema and evidence of diffuse bronchial asthma throughout both lungs.

Skin testing by the scratch method showed the following reactions: tobacco 2+, *Poa annua* (walk grass) 1+, *Atriplex hastata* (fat-hen) 1+, *Lolium temulentum* (Darnel) 1+, *Plantago lanceolata* (English plantain) 1+, *Atriplex patula* (spearscale) 2+, *Chenopodium album* (white goosefoot) 1+, *Salicornia ambigua* (pickle weed) 1+, *Salsola kali* (Russian thistle) 1+, red rose 1+, *Quercus agrifolia* (live oak) 4+,

*The possibility that an allergy or intestinal toxemia arises from the large amount of pine pollen which accumulates in the water of the streams and of the shore lines of lakes in the Sierras during June and July has been commonly held as a cause of attacks of nausea, vomiting, and diarrhea, often associated with fever, which occur at times in an epidemic fashion in these months. It is my opinion, however, that this syndrome results from an intestinal infection arising from the raw or inadequately pasteurized milk produced by local mountain dairies, or from the unfiltered and unsupervised water from the lakes or streams of the area. Allergy to the pollen, especially, can safely be excluded as a cause.

Quercus velutina (black oak) 4+, *Juglans regia* (English walnut) 6+, *Juglans hindsii* (black walnut) 4+, *Platanus orientalis* (oriental sycamore) 2+, *Platanus occidentalis* (occidental sycamore) 3+, *Cupressus marcocarpa* (Monterey cypress) 2+, *Robinia pseudacacia* (locust) 1+, *Pinus radiata* (Monterey pine) 6+, *Pinus monticale* (white pine) 1+, *Pinus attenuata* (knot cone pine) 3+, *Pinus austriaca* (Austrian pine) 1+, *Pinus lambertiana* (sugar pine) 4+, *Pinus muricata* (Bishop pine) 2+, *Pinus ponderosa* (yellow pine) 3+, *Pinus sylvestris* (Scotch pine) 3+, and *Pinus murràyana* (tamarack pine) 3+.

Desensitization with pollens, especially of yellow pine and tamarack pine, and also with live oak, orchard grass, English rye grass, timothy, mountain sagebrush, and Russian thistle over a period of two years and intermittently during the last year has controlled his symptoms so that practically no asthma has been present during the last two years, even during June to September when pine pollens are especially abundant.

DISCUSSION

This patient's symptoms were most marked in June and July when pine pollen is especially abundant and before the mountain sagebrush and Russian thistle are in the air. Yellow pine and tamarack pine are especially abundant over the entire surrounding valley and mountains for miles around. No oaks grow at this 6,000 foot altitude. Thus it is evident that pine pollen allergy played the important part in causing his bronchial asthma in the Tahoe area. The grass, mountain sagebrush and Russian thistle pollens were included in his antigens because of their slight skin reactions. Mountain sagebrush, to which a slight intradermal reaction occurred, covers the entire area for miles around, and Russian thistle is widely distributed, increasing in frequency in the lower regions of Nevada to the East.

This recording of bronchial and nasal symptoms and the demonstration of large typical skin reactions by the scratch method of testing indicate that other cases of such pine pollen allergy probably occur in pine covered areas in this and other countries. Our patient had developed asthma to other pollens and in all likelihood especially to those of oaks which are abundant in Sonoma County before coming to the Tahoe area thirteen years ago. Since then he has lived the greater part of the year in this area where the entire country for miles around is forested, especially with pines. His susceptibility to pollen allergy and his long-continued exposure to pine pollens account for his development of allergy to these. The failure, heretofore, to demonstrate clinical allergy and skin reactions to pine pollens has been explained in part to the large size of the pollen grains.

CONCLUSIONS

Pine pollen allergy productive of bronchial asthma and nasal allergy and associated with large scratch skin reactions is recorded for the first time in the literature.

2940 Summit Street

USE OF WHOLE BEE EXTRACT IN SENSITIZATION TO BEES, WASPS, AND ANTS

HOMER E. PRINCE, M.D., AND P. G. SECREST, JR., M.D.
HOUSTON, TEXAS

IN THE scope of this paper it is not our motive to further the evidence that certain individuals have hypersensitizations to insect stings or to prove that the sensitivities are atopic. Numerous cases have already been reported in which bee-sensitive patients have been successfully hyposensitized with the extracts of the whole bee body,[1] the extract of the body minus the stinging apparatus,[2] or the extract of the posterior one-eighth inch of the body.[3] We wish to cite 3 interesting cases sensitive to insect stings which have given skin reactions to extract prepared from an insect other than that known to cause trouble, and to point out possibilities of hyposensitization with such heterologous extracts. Whole bee extract, standardized on total nitrogen basis, was used in the cases cited below.

CASE REPORTS

CASE 1.—C. O., a 10-year-old male, was first seen August 2, 1937, with a complaint of swelling and hives from insect stings. Two years previously he had been stung by a wasp which caused swelling over his chest, face, and fingers. These symptoms were apparent eight hours following the sting and persisted two or three days. Respiratory symptoms were absent. Since this episode, the stings of bees, wasps, and ants have caused similar swellings. Other allergic history revealed an urticaria at the age of nine months from the ingestion of string beans. Gradual addition to the diet after an elimination period of nine months gave no trouble from further ingestion of the same food. Intradermal testing with 0.02 c.c. of 0.1 mg. total nitrogen per c.c. of whole bee extract gave a positive local reaction. Treatment was begun August 6, 1937, with 0.05 c.c. of the same strength extract and continued through October 24, 1938, at which time he was receiving 0.50 c.c. of the stock (1.00 mg. total nitrogen per c.c.). The first sting after institution of treatment occurred August 23, 1937, after five injections had been received. The patient reported that he had been stung one hour previously by three "yellow jackets" (species *Vespa*) on the right middle finger, the left wrist, and the abdomen, respectively. There was moderate swelling of the right middle finger; the wrist showed a swelling 2 inches in diameter; and there was erythema, 1½ inches in diameter, on the abdomen, but only slight swelling. The left arm gradually swelled halfway to the elbow. On October 10, 1937, he had a bee sting without any ill results. On June 22, 1938, he reported another bee sting with only local reaction, and again on July 13, 1938, he was stung by a "yellow jacket" with little local reaction. On August 2, 1938, he was stung by five red ants with no reaction.

To recapitulate, the original symptoms were noted after a wasp sting, and following hyposensitization with whole bee extract, subsequent stings of bees, wasps, and ants gave no reaction. History implicated these insects as offenders previous to hyposensitization.

CASE 2.—H. L. R., female, aged 38 years, was seen October 13, 1938, with a complaint of "sensitization to wasp stings." In February, 1938, a wasp stung her on the middle part of the right leg and caused her right foot to swell so badly that she was unable to wear a shoe for three weeks. Swelling also involved her right wrist. She was stung again September, 1938, on the left leg below the knee. The swelling was so great at the site of the sting that it caused her hose to tear; her foot was swollen for a week. Physical examination revealed generalized thickened skin, especially marked over her face, and various swellings over her ears, eyes, lips, and body, with itching. This second occurrence was much more severe than the first. Her past history relative to insect stings revealed several wasp stings, with no effect in childhood. She had been stung by various types of ants which caused moderate wheals. To her knowledge she had never been stung by a bee. Other personal and family history of allergy was negative. She was skin tested with serial dilutions of whole bee extract with questionable local reaction to 0.001 mg. total nitrogen per c.c., followed by an itching sensation and urticaria of her face which cleared with adrenalin. An attempt was made to hyposensitize her, beginning with 0.20 c.c. of 0.000001 mg. total nitrogen per c.c. extract. Following an injection of 0.9 c.c. of this extract six weeks later, she experienced swelling of her neck and arms, which cleared completely upon temporary discontinuation of all injections. At the time of this report she is being started on injections of whole bee extract again with a still further dilution to 0.000000001 mg. total nitrogen per c.c., and so far is tolerating the injections without trouble.

In this patient symptoms began, following a wasp sting. Within seven months a second wasp sting resulted in further symptoms. When she was tested with bee extract in high dilutions, she experienced a mild systemic reaction. A similar reaction also followed the ninth of a series of prophylactic injections.

CASE 3.—D. F. H., a 46-year-old male, presented himself to the Allergy Clinic of the Southern Pacific Railroad Hospital October 11, 1938, with a complaint of hives since the sting of a wasp two months previously. This was the first wasp sting that he had received in several years. Earlier wasp and bee stings had given him no trouble. Six months before the present symptoms began he was stung by a bee which caused marked swelling at the site of the sting on the wrist. He was skin tested with whole bee extract and found to react to 0.1 mg. total nitrogen per c.c. dilution. Hyposensitization was instituted with the reacting dilution, and his condition immediately improved. Improvement was steady and marked until he received 1.00 c.c. 0.1 mg. total nitrogen per c.c. dilution, the seventh injection, following which he had generalized urticaria.

Case 3 is an instance of urticaria precipitated by a wasp sting. History of previous wasp sting was of no consequence, but a bee sting six months previously caused considerable swelling at the site of the sting. Hyposensitization was started with whole bee extract. The symptoms had practically disappeared until the patient received a therapeutic overdosage which resulted in generalized urticaria.

Cases 2 and 3 have not been hyposensitized to a sufficiently high degree to assume clinical protection and they have received no sting as yet. Both patients are being continued on reduced dosage in the hope such protection will eventually be secured.

DISCUSSION

We would like to point out the zoologic classifications[4] of the wasp, yellow jacket, bee, and ant as follows:

Phylum *Arthropoda* Body with series of segments, some or all bearing jointed appendages, covered by a chitinous exoskeleton. In the body is a central tube. This is the alimentary canal with anterior mouth opening and posterior anal opening. Ventral to the alimentary canal is the nerve cord and dorsal to it is the heart.

Class *Insecta* Antennae and three pairs of legs are present; representatives usually have wings and are air breathing.

Order *Hymenoptera* Four membranous wings with few veins; the first abdominal segment is fused, or partly fused, with the thorax. Mouth parts are both mandibulate and suctorial. Female has an ovipositor developed as a sting in the bee, wasp, and ant. Metamorphosis is complete.

Suborder *Clistogastra*

Family *Apidae Apis mellifica* (honeybee)

Family *Vespidae Vespa* spp. (yellow jacket and other "Social wasps")

Family *Formicidae* spp. (mixed ants)

We suggest that the extract of the bee *(Apis mellifica)* will hyposensitize human beings against species of other families in question of the suborder *Clistogastra* of the order *Hymenoptera*, of the class *Insecta*, phylum *Arthropoda*. Symptoms of overdosage in Cases 2 and 3 suggest that we are dealing with identical or closely related antigens. Unfortunately, ideal subjects, conditions, or reports for this particular type of experimentation are not easily available and may require some years of waiting. This presentation of three cases and comments are offered as a preliminary report until further evidence can be supplied. If we are correct in believing that treatment with antigen prepared from one insect of this group confers protection against the other closely related insects, the problem of securing material for therapy is much simplified.

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PERIPHERAL NEURITIS: ALLERGY TO HONEYBEE STINGS*

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THERE are many reports in medical literature of sudden, profound, generalized, shocklike reactions following bee and other insect stings, but as far as the author can determine, the following case is the first to be recorded of peripheral neuritis as a complication of bee sting.

Most instances of allergic manifestations in nerve structures involve the central and autonomic systems. The dramatic constitutional reactions following insect stings fall into this group. That the peripheral nervous system also can be implicated allergically has been shown by the neuritides following serum injections (Richardson,[1] Kennedy,[2] Dyke,[3] Bennett[4]). Kennedy[5] wrote of migrating palsies, apparently due to sinusitis, in a man with an inherited allergic disposition. Mackay,[6] and Campbell and Allison[7] described peripheral neuritis in patients having recurrent urticarial attacks of unknown etiology. Mathieu[8] presented the case of a man who developed unconsciousness, respiratory difficulties, and a right brachial plexus palsy after the ingestion of crab meat. The following case is another illustration of allergic involvement of the peripheral nervous mechanism.

CASE REPORT

W. T., male, aged 34 years, an employee in the laundry of the Michigan State Hospital for Epileptics, and an apiarist by avocation, was examined June 15, 1938, because of swelling and paralysis of the right hand.

Significant Past History.—When the patient was 10 years old, he fell 16 feet and landed in a sitting position. He was paralyzed and anesthetic below the hips for almost a month. At 29 years he had some urinary disturbances suggestive of cystitis, and at that time had an incoordination in walking; his legs were weak; he would not know where he was placing his feet; and there were paresthesias in the lower extremities. There was gradual improvement so that in four months he had returned to normal. There had been no recurrences of such difficulties. He had never had any ocular disturbance. There was absolutely no history of allergic disorders in the patient or in his family.

Present Illness.—For several years he had handled yellow jackets, hornets, and honeybees, and although stung frequently, had had merely a little local reaction. During the past two years he had his own hive of honeybees. During 1937 he had no serious reaction following their stings. Between August, 1937, and May, 1938, he was not stung by the bees, but in the last week of May he was stung several times on the right hand, and for two days his right forearm was markedly swollen, but there were no motor or sensory disturbances. However, he did notice some shortness of breath,

*From the Michigan State Hospital for Epileptics, Wahjamega.

especially on exertion. He recovered completely, but on June 12, 1938, he was stung seven times on the right arm, four on the left, about ten on the chest and a few times on the legs. The left hand swelled only slightly for a day. However, the right hand swelled immediately and within eighteen hours the entire forearm was markedly swollen. He developed weakness of grip and numbness of the entire hand, but had no pain. For two days after being stung he complained of headache, dizziness, tinnitus, anorexia, generalized fatigue, and a feeling of constriction about the chest.

Physical Examination.—A detailed medical and neurologic examination disclosed no significant abnormalities, except the affection of the right upper extremity. The right hand was slightly swollen, being 1 cm. larger in circumference than the left. Motor involvement showed slight weakness of the triceps, and extensor carpi radialis and ulnaris, and more evident weakness of the extensor digitorum communis; paresis of flexor carpi radialis and ulnaris, and supinators and pronators of the forearm; and pronounced weakness of the interossei, lumbricales, flexor digitorum sublimis and profundus, and opponens pollicus. Sensory involvement revealed hypalgesia, thermhypesthesia, hypesthesia affecting the entire right little finger, the midportion of the dorsum of the right middle and ring fingers, and a patch over the dorsum of the forearm; loss of vibratory and of motion and position senses of the right little finger. These alterations in function involve the radial, median, ulnar, and dorsal antibrachial cutaneous nerves.

Laboratory data were normal other than a blood eosinophilia of 7 per cent.

On June 18, 1938, the sensory changes had all disappeared, but there was still some weakness of the affected muscles. By June 25 strength was normal in all groups.

On July 5 the patient was stung twice on the left hand, and on the following day the left forearm, hand, and fingers were swollen, but there were no sensory changes or definite evidences of muscular weakness. The white blood count was 8,500 cells with 5 per cent eosinophiles; otherwise the differential count was not remarkable. On November 4, 1938, scratch and intracutaneous tests with Miscellaneous Allergenic Bee Extract (Lederle) 0.001 and 0.0001 mg. nitrogen per c.c. were negative after one-half hour and eighteen hours, respectively. The patient had attempted to immunize himself with single stings several times since July.

DISCUSSION

The neuritis was apparently allergic. The history of frequent previously uneventful encounters with bees, the mild dyspneic attack after being stung in May, 1938, another bee attack two weeks later rapidly followed by constitutional symptoms, neuritis, and eosinophilia, all point to an allergic factor. It is probable that a perineural urticaria caused a temporary physiologic block of nerve function or "compression neuritis."

With respect to what the patient was allergic to, Benson and Semenov[9] consider three factors in bee stings: (1) the venom, (2) allergic reactions caused by pollen adhering to the bee, and (3) allergic reactions from sensitization to allergens inherent in the bee.

Pure honeybee venom apparently "represents a combination of lecithin with basic radicals resembling in some respects sapotoxins and cantharadin" (Wells).[10] Histamine is also present and is undoubtedly concerned in causing the vascular cutaneous reaction (Marcou and Derevici[11]). Each bee yields about 0.0001 gm. of venom, the protein

fraction of which must be minute. It is rather unlikely, therefore, that the neuritis here reported was due to hypersensitivity to the venom alone.

The possibility that the bee injected pollen adhering to its body, and to which the patient was sensitive, is remote, since the anatomic structure of the stinging apparatus is such that "the lancet is almost entirely free from contamination with pollen" (Benson and Semenov[9]).

The neuritis represents a hypersensitivity to allergens inherent in the bee. This is the most likely explanation. When a honeybee stings, the entire stinging mechanism, consisting of lancet, poison sac, and acid and alkaline glands, is left behind in the victim's flesh. Benson and Semenov[9] have shown conclusively that the extracts of this apparatus, as well as of the stingerless body of the bee, can produce positive skin tests in individuals sensitive to these allergens. Although in the patient herewith reported an allergenic honeybee extract did not cause a local skin reaction, it is to be noted that he had attempted to immunize himself with single stings on several occasions between the time of his neuritis and the time the tests were made.

SUMMARY

A case is reported of peripheral neuritis apparently due to hypersensitivity to allergens inherent in the honeybee (*Apis mellifica*).

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A NOTE ON A NEW METHOD OF PRESERVING POLLEN AND DUST EXTRACTS*

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THERE are some objectionable features to all of the methods of preparation of pollen and dust extracts which are in use at the present time. Those made in a buffered saline menstruum lose their potency fairly rapidly and must be restandardized at frequent intervals. Those made in glycerinized saline, while they retain their potency for long periods of time, are painful when used for treatment and must be diluted in saline for intradermal testing. Glucose extracts are more difficult to prepare and are easily contaminated.

An ideal extract should be potent, should remain indefinitely without appreciable change in potency, should be capable of being used for testing and for treatment, and should cause no pain on injection.

Experience with the lyophile method of drying sera and other substances used in immunology led to an attempt to use this method in preserving pollen and dust extracts. This was made possible by the demonstration by Ecker and Pillemer[1] that vacuum desiccation can be carried out in a very simple apparatus the cost of which is less than $100.00.

Pollen or dust extracts are prepared in saline or buffered saline and are standardized according to the method of one's choice. The Seitz filtered extract is distributed in bottles in the amount usually needed each two weeks (in our practice 30 c.c.) The number of bottles holding a total volume of 60 c.c. are placed in the desiccating chamber and are dried completely overnight. In the morning the chamber is opened, each bottle is capped with a rubber cork and is placed under high vacuum by drawing off the air through a needle which is plunged through the rubber cap and is connected to the vacuum pump. The bottles of extract suitably labelled are stored in the icebox until needed.

When one desires to use a new bottle, one adds the required amount of water to the desiccated material with a syringe. The dry material dissolves completely and has a potency unchanged when compared with the original material.

Since we have adopted this method of preparation of pollen and dust extracts, we have been able to have fresh new solutions each two weeks without the necessity of repreparing and restandardizing at frequent intervals. If one purchases a large supply of pollen, it is practical to make, dehydrate, and store sufficient extract for a year's use at one time.

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*From the Asthma and Hay Fever Clinic, Cleveland.

Society Proceedings

SYMPOSIUM ON ALLERGY AND EDUCATION*

RICHARD A. KERN, M.D., PRESIDING

INTRODUCTION

THE past twenty-five years have witnessed a truly remarkable growth in the clinical implications of allergy. From the narrow field of the laboratory, the concept of hypersensitiveness has broadened until it now touches practically every phase of clinical medicine. This rapid growth of clinical allergy has raised many problems quite apart from the strictly scientific aspect of the subject; problems which have to do with various phases of the dissemination of information about allergy and with the application of this knowledge in practice. They are problems with which every allergist has had some contact, and with which especially those who are teachers have had to wrestle early and late. Even the special societies devoted to allergy have found it necessary to take action toward the solution of some of these problems: witness the activities of their Joint Committee on Standards.

Yet the discussion of these matters has rarely been more than the casual exchange of ideas between two allergists on chance contact, or the subject of wrangling in a committee meeting. Almost never have our ideas on these things been aired in an open meeting or appeared in print.

The time, therefore, seemed ripe to devote a whole program rather than a few minutes in a perfunctory business meeting to a consideration of some of these matters. This would have the further advantage that the material might be presented by speakers selected for their known qualifications, and whose remarks would be the result of sober reflection, rather than the snap judgments of an unpremeditated discussion.

Two symposia were, therefore, arranged, the first dealing with *Allergy and Education* as it concerns the medical student, the general practitioner, the allergist, the specialist, and the layman; and the second dealing with the *Practice of Allergy*, both in the clinic and in private practice.

A significant comment on the interest of allergists in such a program is the fact that every one of the eleven men who were invited to take

*One of two symposia presented at the Fall Meeting of The Society for the Study of Asthma and Allied Conditions, New York, N. Y., December 3, 1938.

part in these symposia promptly accepted. They are all here today, with the exception of Dr. Leslie N. Gay, who became ill this week. His associate, Dr. Nathan Herman, has, however, kindly consented to take his place.

DR. KERN.—There is no question that allergy must be taught to our medical students: even the Dean and the Curriculum Committee will admit that. The question is rather, how much should the undergraduate learn about allergy? The symposium will, therefore, begin with the presentation of the subject

Allergy and the Medical Student. LOUIS TUFT, M.D., Philadelphia, Pa.

Uniform agreement exists at present as to the importance and the necessity of including adequate instruction in allergy in the medical curriculum. Up until recently the amount of instruction given was rather slight, since the subject of allergy was not considered important enough to warrant detailed instruction. As a rule, one or two clinics or lectures on hay fever and asthma and possibly some reference to the subject in the course in bacteriology were considered adequate for the medical student.

The increasing recognition of the importance of allergy and its widespread application to so many clinical conditions and so many specialties in medicine, has led to a desire for an increase in the amount of instruction considered essential in the preparation of the medical student for general practice. The work of the Committee on Standards of both societies has no doubt been helpful in emphasizing this need.

The only question that might be considered controversial at present concerns the amount of instruction which the medical student should receive and the course in which it should be included. The answer to this depends upon whether or not it is considered necessary that the medical student be given sufficient instruction to enable him to cope with the ordinary problems of allergy met with in general practice, or whether his instruction should be limited to essentials only, so that the allergist would have to be the one to take care of most of these patients. Even though it might be considered ideal to have all patients with allergic diseases treated by those who are especially qualified to do so, the situation in practice today is such that the majority of these patients must of necessity be treated by the general practitioner. It seems to me, therefore, that in order that these patients receive the proper treatment it is our duty to attempt to teach the practitioner how to treat these cases intelligently and not expect to have the specialist take care of all of them. There is no more reason why the practitioner should not be able to treat allergic diseases as well as he treats cardiac diseases. No cardiologist expects that cases of cardiac decompensation should be treated by the specialist and not by the practitioner. All students are taught how to care for ordinary cardiac cases, and most of them accomplish this in excellent fashion. On the other hand, when they meet with difficulties in diagnosis or treatment, or where specialized knowledge or examination is necessary, as for example in a case of bundle branch block, they always turn to the cardiac specialists for help.

Adequate instruction in allergy should most certainly be given to the practitioner, therefore, and the best time to do it is in the embryo or medical student stage, and not after he has been in practice for a good many years. It is much easier to teach him as a student than after he has become a busy practitioner. To use a crude simile, the best time to treat syphilis is in the primary stage rather than in the late or tertiary period.

The ideal program of instruction, it seems to me, would consist of instruction in the fundamentals and general principles of allergy in the preclinical years, preferably in the course in Bacteriology and Immunology. This is very similar to giving instruction in pathology during this period as a foundation stone for internal medicine. Instruction in the clinical manifestations and practical clinical experience in the out-patient clinic should then be included as part of the course in medicine in the junior and senior years. To illustrate this program, I should like to present a résumé of the instruction given in allergy at the Temple University Medical School. This consists of the following:

Sophomore Year (1st Trimester)

Course—Bacteriology, Mycology, and Principles of Immunity

2 lectures (one hour each) on principles of anaphylaxis and allergy

2 laboratory periods (two hours each) for performance of precipitin tests and demonstration of anaphylaxis by Dr. John A. Kolmer, Professor of Medicine in charge of Bacteriology and Immunology.

Sophomore Year (3rd Trimester)

Course—Advanced Immunology

2 lectures on allergy giving the more intimate and clinical phases by Dr. Kolmer

2 clinics on allergy to illustrate these lectures by Dr. Tuft

Junior Year

Course—Biologic Therapy

2 lectures on specific treatment of allergic diseases by Dr. Kolmer

Senior Year

Course—Medicine—in charge of Dr. Charles L. Brown, Professor of Medicine

12 lectures covering entire subject of allergy, reviewing general principles and clinical manifestations given at outset of year by Dr. Tuft

3 periods (one and one-half hours each) in out-patient clinic of allergy and applied immunology to sections of 6 to 7 students. Students are allowed to take an allergic history, do skin tests, and treat *ordinary* types of allergic diseases, all under supervision of Dr. Tuft and his associates.

It is believed that this program of instruction will give the graduate of a medical school sufficient knowledge of the subject to enable him to diagnose and treat properly those allergic conditions which he is likely to encounter in ordinary practice. Contact with students who have taken this course of instruction convinces me that the amount of time spent has been greatly appreciated and that this type of instruction will equip the practitioner to diagnose and treat allergic diseases in far better fashion than most of our practitioners are able to do at present.

DR. KERN.—Of the 7 of us at this table, 4 had never heard the word "allergy" in their undergraduate days, and the other 3 certainly received no formal instruction in the subject. That is exactly the status of the majority of men in medical practice today. Can anything be done about it? There will now be presented the topic

Allergy and the General Practitioner. HARRY L. ALEXANDER, M.D., St. Louis, Mo.

There are, presumably, several million patients with allergy in the United States and at best but a few hundred qualified allergists. Under these circumstances, to treat allergy adequately would require either more specialists in this field—thousands of them—or more instruction for those who now treat most of these patients, namely, the general practitioner, the otolaryngologist, dermatologist, gastroenterologist, and the pediatrician.

The first alternative would seem the less feasible. Facilities for instruction in allergy are as yet not sufficiently organized to train a large number of individuals, and many years would necessarily elapse before such a program could be accomplished.

To provide the general practitioner and others with sufficient and correct information concerning the proper care of allergic individuals could at best be of limited value. However, with proper organization for dissemination of instruction much may be accomplished. With such a program it should be recognized that at first only essential principles stated in the simplest terms should be offered.

The point could then be made that most patients who seek medical attention have symptoms continually or, at least, frequently. Since there are comparatively few allergens to which exposure is common, a list of these offending substances would be prepared. Then the principles of an antiallergic regime would be described, with emphasis on the fact that unless sufficient exposure occurs, symptoms of allergy are not possible. The preparation of the bedroom, substitutions for orris, pyrethrum, and other common offenders by relatively nonallergic substances, and the principles of elimination diets with details of their preparation, could be stated simply.

The proper preparation of an antiallergic environment to eliminate common allergens insofar as possible should benefit most patients with asthma, vasomotor rhinitis, gastrointestinal allergy, and other related disorders in which pollens or occupational dusts and similar etiologic agents are not involved. This approach alone, without the use of skin tests or other specific laboratory procedures, may be sufficient to prepare the practitioner for more advanced instruction to come. After all, the allergist depends most on his ability to detect offending substances and insure their removal from the patient's environment. So often the allergen at fault is not detected directly but only by trial, after general elimination measures have been instituted. The details of such a program should be available to all. Patients who do not respond may then be referred to an allergist.

At present, the general practitioner, who is willing to learn to treat cases properly, finds difficulty in getting simple and precise instruction, for, as several have told me, the lectures they hear and articles they read are confusing rather than clarifying. He then does the best he can with symptomatic treatment. Some perform skin tests and

interpret every positive reaction as representing an active etiologic factor, and then give hyposensitizing injections according to printed instructions.

Once those who would learn have absorbed the preliminary instruction suggested, the more advanced processes of differential diagnosis, skin testing with its proper interpretation, the correct methods of hypodermatic treatment, etc., could be offered.

Such a program as this would require, first, a committee or board of instruction created by this or some other society that could call upon experts. It would depend upon trained allergists to disseminate uniform instruction before local medical societies that, having been circularized, then request it. Printed literature would be available to all.

Although any pretentious plan of gratuitous instruction usually falls far short of its intention, nothing seems more damaging to the reputation of allergy than the unenlightened treatment that patients too often receive under the present status of management by those not properly informed.

DR. KERN.—The most important phase of allergy in education is that which has to do with the training of those who wish to specialize in this field. The symposium continues with the discussion of

Training the Specialist in Allergy. ROBERT A. COOKE, M.D., New York, N. Y.

Adequate reasons have existed for the trend toward specialization in medicine and surgery, otherwise it could not have developed. It has been a natural sequence of the rapid accumulation and diversity of medical data and the technical requirements in many of the methods of diagnosis and therapy combined with an unquenchable thirst and an irresistible desire for clinical or experimental exploration into details of each and every disease or group of diseases.

Occasionally entirely new fields are opened as a result of a new concept of disease processes. The concept of sensitization, crystallized in the early years of the present century, satisfactorily explained many of the phenomena of previously unexplained diseases, and thus "allergy," the newest and latest of the special fields of medicine, was born. It has become a special field for the very reasons mentioned, namely, the rapidly accumulating data, certain technical refinements, and the unlimited possibilities for medical investigation.

Those of us who have been interested in allergy are naturally concerned with the training of future allergists, for we remember only too well the early and almost insuperable difficulties that were encountered as a result of our ignorance and the lack of proper facilities. The time has come for concerted effort more effectively to organize existing facilities and to create better ones for students of allergy so that its advance may be promoted safely and sanely. I do feel that allergy, to date, has been kept on a sound and even keel; unworthy attempts at exploitation here and there have been largely repressed. As to its future, I believe that the advances will be more rapid, more fundamental in character, and broader in scope, if we can secure for those who are to carry on, a better training in allergy and better facilities for clinical and research work.

Before discussing the question of special training, there are two points that should be kept clearly in mind. First, that there should be no attempt to specify details of training, no hard and fast rules should be drawn that savor in the slightest degree of regimentation. Rather, I believe, we should attempt to create better facilities for those whose interest and aptitude lead them to utilize the opportunities that have been opened to them.

The second point deals with the question as to whether allergy is properly a specialty and whether it will remain such. Based as it is upon a broad biological principle rather than upon anatomic or functional entity, as most specialties are, I think the query is a valid one. As to its permanency I have not been able to satisfy myself, but at least it seems safe to say that its future is assured until such time as its fundamentals are much better understood.

Assuming then that for the present there is such a specialty as allergy, to what extent do we need allergists and what purposes would they fulfill? With the minimal training in allergy in medical school today, the general practitioner is able to diagnose and treat the simpler forms of allergy and short "refresher" courses even now available will serve to keep him up to date.

The accepted practice of the specialist today will be routine practice for the practitioner of tomorrow. But allergy is a relatively new field, relatively little of its fundamentals is known. If the cause and nature and ultimately the prevention of the sensitization mechanism are to be probed to their depths, then there must be a need for a special group of well-trained, scientifically-minded physicians whose purpose it will be to carry on the investigations that will advance the knowledge of allergy and its application in general practice. Such specialists would have a field of usefulness in medical schools and as heads of clinics with research facilities. It is to the training of this rather limited group that my remarks are directed. The term "allergy specialist," then, is used to designate not those who devote their time to the treatment of many allergic patients, but rather those who devote their time, their minds, and their energies to the solution of the problems of allergy.

Training of Allergists.—The training in allergy, as for any special field of medicine, should rest upon the firm foundation of adequate training in internal medicine. It matters not just how this experience is gained, but if time is not to be lost, it can be readily obtained by intensive application, following graduation from medical school. The two years' internship, followed by a two- or preferably three-year residency, would certainly fulfill the requirements. For those whose interest attracted them to allergy, the third year as resident could profitably be used for extra application in chemistry, bacteriology, and immunology.

The opportunities for adequate training in allergy are not as numerous today as they should be. There seem to be now but two avenues open to the prospective allergist: one, the research fellowship, of which there are few; the other, an association as assistant with an allergist who has proper clinical and laboratory facilities. Three years so spent would, I believe, afford sufficient experience to qualify one as specialist in allergy at the average age of 34.

A word is needed as to what should be regarded as adequate facilities. The ideal department of allergy should consist of a clinic with

out-patient and ward facilities, having an adult and a pediatric service for medical and dermatologic cases, a special and intimate connection with rhinology, and a consultation service for the study of all types of cases referred by any and all of the other hospital services. The student allergist should be given full opportunity to diagnose and treat all types of allergic manifestations and should be required for at least six consecutive months to serve twice a week in the general dermatology and rhinology clinic for the purpose of diagnostic training. The laboratory is as important as the clinic. It must be equipped for routine work and for research in chemistry, immunology, and bacteriology. A department of allergy so organized and carefully and energetically directed should be able to graduate at least one three-year student allergist each year.

Recognition.—The Board of Internal Medicine requires six years of study after graduation from medical school in order to qualify for examination as internist. After the first year of work in allergy with the background of two years' internship and three years' medical residency, the examination for certification in internal medicine should be taken. The question is what recognition, if any, should be given to the man who satisfactorily completed the three years in the study of allergy since certification in special fields of medicine has not yet been undertaken by this Board. I do not feel that any attempt should be made by the national allergy societies to organize an independent board of certification by examination as many other such societies representing special fields of medicine or surgery have already done. The Board of Internal Medicine has this important move under consideration, and the work would be much better done by such an independent body. Pending such a development, it is my thought that some recognition might well be made by the national societies interested in allergy. My suggestion is that they should prepare to recognize as perhaps "Fellows" or "Specialists" in allergy, through the recommendation of the existing joint Standards Committee, those physicians who have satisfactorily completed at least three years of special training in certain approved clinics upon the presentation and acceptance of a thesis involving original work in allergy.

DR. KERN.—In the majority of instances allergy lies in the field of internal medicine. The commonest development has, therefore, been that an internist becomes secondarily an allergist. But allergy extends into many medical specialties. In two in particular has allergy practically become a specialty within a specialty: otolaryngology and dermatology. The training of the allergist in these special fields has its own problems and implication. We now consider

Allergy and the Specialties: Otolaryngology. HARRY P. SCHENCK, M.D., Philadelphia, Pa.

Only fifteen years ago, otolaryngologists were "curing" bronchial asthma by nasal surgery and regarding allergists as dealing in something akin to Abrams' electronic machine. Infection was the cause of most nasal symptoms and the idea that sensitization to otherwise innocuous substances might at times be a cause was, to say the least,

ludicrous. Surely the rhinologist knew more about the upper respiratory tract than did a few visionary internists and eccentric immunologists who had coined a new word—"allergy." On the other hand, the allergist frankly regarded the rhinologist as a sadist, reveling in surgical procedures, as an idolater, worshiping at the shrine of the sphenopalatine ganglion, or merely as a plumber, dealing in matters of obstruction and drainage.

The proficiency of the rhinologist in dealing with the problems of allergy has developed through years of intimate association and prolonged cooperation with the allergist, until today, there has practically developed a specialty within a specialty: the rhinologic management of allergic individuals.

In the light of our present knowledge, what should the allergist expect and demand from the rhinologist to whom he entrusts the welfare of his patients?

First and foremost, he should demand that the rhinologist possess at least some knowledge of allergic investigation, diagnosis, and treatment. Thus he will come to appreciate the limitations as well as the possibilities of diagnostic procedures, such as scratch, patch, and intradermal tests, and dietary regulation. He will then become aware that not only the nose and sinuses but many other shock organs may be involved by the systemic condition known as allergy. He will, in many instances, be convinced that desensitization alone may be far more effective than surgical measures.

The allergist should demand of the rhinologist a clear understanding of the tissue changes and the alterations in secretions of allergic patients. He should, whenever possible, be able to differentiate between tissue changes due to allergy alone, to infection alone, or to both.

The rhinologic examination of the allergic patient must be meticulous, particularly with the nasopharyngoscope and the transillumination bulb. The clinical findings should then be checked with the roentgenologic findings, and the roentgenologist will benefit by being present if surgical intervention follows.

The report of the clinical examination should be itemized to include negative as well as positive findings. This ensures inspection of all areas and deprives the rhinologist of an alibi when the x-ray report comes through. The location of reactions in the upper respiratory tract is important and should be noted. To some extent, the effects of inhalants and foods are manifested in different nasal areas, thus providing earlier diagnosis and possibly earlier relief of the patient.

In the presence of anatomic variations or structural abnormalities in the nose or sinuses, the rhinologist should act, not on the basis of their effects in average patients, but on the basis of his and the allergist's experience of their effects in allergic individuals.

The rhinologist is in an excellent position to evaluate the effects of allergy measures upon the upper respiratory tract by frequently reexamining the patient. Therefore, re-examination at regular intervals should be routine. The experienced rhinologist is loath to operate upon allergic individuals because he has learned that, without control of the underlying allergy, recurrence of polyps and abnormal tissue is inevitable. The rhinologist who is able to follow a few thoroughly studied cases will acquire more experience than one who sporadically follows many cases, poorly handled from the allergy standpoint.

Because of the technical difficulties of otologic practice, the allergist must depend largely upon the otolaryngologist for guidance, but the allergist may confidently insist that the otologic importance of allergy has not been sufficiently stressed.

Finally, may I point out to the allergist that there remain a few rhinologic problems which cannot be solved on an allergic basis. Allergy measures sometimes fail and the welfare of the patient may depend upon the establishment of physiologic integrity of the nose and sinuses. This then becomes a rhinologic problem. Moreover, in the presence of chronic infection, major anatomic defects or deformities, inadequate rhinologic intervention may impede or even negate all the efforts of the allergist.

DR. KERN.—The discussion is continued from the viewpoint of

Dermatology: The Dermatologic Training of Allergists. MARION B. SULZBERGER, M.D., New York, N. Y.

When I accepted the invitation of our Chairman, Dr. Kern, I did so with the full realization that a truthful and vigorous expression of my opinion on this subject might not make pleasant listening to all allergists. I hope, however, that the truth of what I shall say will be so evident to all here that it will not estrange or shock the many friends I see among this audience.

When one considers the bases for the division of medicine into its various specialties, one is struck by the practical but essentially unscientific nature of the boundaries. Pediatrics, for example, is bounded by the criterion of the age of the patient; the fields of the surgeon, of the roentgenologist, of the physical therapeutist—all are determined by the modalities employed; the spheres of the syphilologist and of the tuberculosis specialist include all manifestations attributable to the respective etiologic agents; the province of the venereologist embraces those diseases which are usually acquired through sexual exposures; and, to terminate an enumeration which would prove more tedious than profitable, the specific organ or part affected determines the domains of many specialists, such as those of the proctologist, the gastroenterologist, the ophthalmologist, the neurologist, the otolaryngologist, and the dermatologist.

There are still other specialties—such as serology, pathology, immunology, and allergy—each of which deals with certain fundamental biologic phenomena, phenomena necessarily affecting every organ, every age group, and almost every form of disease. By their very nature these fundamental specialties will include certain manifestations in all the other specialties; and will include the diseases treated by those specialists whose boundaries are determined by the age of the patient, by etiologic agents, by the modalities employed, or by the organs affected.

I am convinced that the specialty of allergy will be able to fulfill its proper function as one of the fundamental specialties in medicine only if allergists concern themselves with *all* the manifestations which are due to specific immunologic changes. They must know more about sensitizations and desensitizations of the eyes, the nose, the lungs, the bone marrow, the gastrointestinal tract, the nerve tissues, the liver, the heart, the epithelia, the vascular structures—in short, they must know more of the allergy of every tissue, every system, and every

organ than does any other specialistic or nonspecialistic practitioner in medicine. The specialist in skin diseases is no exception; this statement applies in full force to allergy in dermatology.

However, when one considers the great number of different skin diseases, one is likely to be astonished at the relatively small number of the dermatologic entities which have, until now, been proved to be based on allergic reactions. And when one further considers the proportion of the proved allergic skin diseases which can be "cured" or even materially benefited by the methods of allergy alone, the figure becomes negligible.

Atopic dermatitis (including infantile eczema) is one example of cutaneous disease almost certainly based on allergic reactions—and yet here the majority of cases cannot be helped by specific desensitization, and even elimination of allergens is often impossible and frequently of relatively little value, except in babies and young children.

In contact-type allergic eczematous dermatitis the discovery of causal allergens is sometimes possible (about one-third of the cases in my material)—but often only after long and careful study—study in which skin tests frequently play only a small part. Even in these proved cases specific desensitization is generally of no practical value (e.g., occupational contact type dermatitis, dye dermatitis, dermatitis from local anesthetics, etc.), and relief through the elimination of allergens is possible in only a certain comparatively small number of instances.

The same remarks apply with equal strength to allergic drug eruptions, except that here not only is desensitization usually impossible but skin tests are almost universally of no value. There is surely no need to tell this particular audience that in the majority of cases of chronic urticaria neither our present methods of skin testing nor those of desensitization therapy are worthy of serious consideration.

It, therefore, becomes apparent that in spite of the brilliant results which can be obtained through the finding and elimination of allergens in a certain number of cases, he who relies exclusively on the methods of allergy will find himself in a very weak position indeed in the treatment even of recognized allergic dermatoses.

The inevitable conclusion is, therefore, that those physicians who treat allergic skin diseases must always be fully competent to treat these same diseases also by every other modern dermatologic and general method; they must be able to apply these methods at once, before the start of the allergic investigation; they must be able to regulate and maintain the treatment during the period of the allergic investigation; and they must be able to continue to apply the best dermatologic methods when and if the "allergic approach" yields little of practical value.

In other words, the immediate application of correct dermatologic methods is essential in every form of cutaneous disease, be it allergic or nonallergic in nature. Unless this is done, many a dermatosis, which might have been checked by adequate early management, will become chronic or perhaps even incurable.

If early proper dermatologic management is so absolute a requirement even in the skin diseases at present recognized as being based on allergy, it is, of course, obvious that dermatologic, and not allergic, approaches are the ones indicated and effective in all the other skin diseases. I have already said that these cutaneous entities in

which allergic studies are, from the practical viewpoint, contraindicated are exceedingly numerous. Many of the dermatoses in which allergic studies are not indicated are often extremely difficult to differentiate from those skin affections which warrant allergic studies. Therefore, he who would manage allergic skin diseases—manage them alone and without help of a specialist in dermatology—must know how to cull those few dermatoses which are amenable to the methods of allergic study from the vast number to which the present procedures of allergy are not applicable. In other words, he must be *fully proficient in dermatologic diagnosis and differential diagnosis.*

My opinion as just expressed may now be summarized as follows: *the independent and adequate management of allergic skin diseases requires a full knowledge of dermatologic diagnosis and of dermatologic therapy plus a special knowledge of the allergic and immunologic aspects of dermatology.* It is certain that today the average dermatologist does not possess the full amount of necessary special knowledge of allergy; it is equally certain that the average allergist is not equipped with the essential dermatologic knowledge.

How long would it take for the allergist to acquire this minimum of necessary knowledge of dermatology? The answer to this question can be given only in the terms of the minimum requirements for specialization both in this country and abroad—namely, from three to five years' "full-time" training in the specialty.

Now if this is the length of time required for an allergist to acquire the minimum knowledge necessary for the competent independent handling of allergic skin diseases, it is more than probable that a full-time period of many months or years would be required to acquire the minimum proficiency in each of the other specialties—such as otolaryngology, ophthalmology, hematology, or gastroenterology. Obviously, no allergist can devote such a staggering sum of years to training in the other specialties. What then is the alternative? I believe the practical alternative has been indicated in my opening statements. The allergist must become a *consultant* specialist. Except in the few conditions—such as hay fever—in which the diagnosis is usually apparent and unequivocal and the management almost exclusively confined to specific measures, the allergist need not be able to diagnose and to treat, but need only be trained to be able to aid and supplement the diagnosis and treatment. The allergist should be able to respond to the calls of his colleagues by supplying the necessary special advanced knowledge in the field of allergy as applied to all the various specialties. Just as the dermatologist cannot be expected to possess a mastery of allergy, so the allergist cannot be expected to master dermatology. But these two specialties must complement and supplement each other. The allergist of the future must be specially trained, not in dermatologic diagnosis and treatment, but in the special procedures of allergy as applicable to dermatology. In this way he will be in a position to assist when called upon in any case in which the diagnosis, or at least the presumptive diagnosis, of "allergic dermatosis" has been established; he will be able to recommend and also to execute the specialistic allergic procedures of diagnosis and therapy which go beyond the capabilities of the average dermatologist—and which will in many instances prove of decisive value only when properly combined with the other dermatologic procedures.

In what way can the allergist acquire the necessary special knowledge of dermatologic allergy—the special knowledge which will enable him to make available and to apply to the proper cutaneous conditions the correct measures and modalities of the specialty of allergy? If and when courses are established in which dermatologic allergy is taught with the express purpose of training allergists, it appears to me that one year devoted to this purpose should suffice. Unfortunately, no such courses are today available, but I believe that the cooperation of departments of dermatology with those of allergy and immunology could develop such courses for post-graduate training. A composite two or two and one-half years' post-graduate course in allergy in relation to all the other specialties, including dermatology, would probably serve to develop allergists who would make the most valuable consultants and who would undoubtedly be of the most material assistance to all their fellow practitioners.

It is at least certain that the average dermatologist has had neither the time nor the opportunities, and does not, therefore, possess the equipment for penetrating sufficiently deeply into the allergic aspects of many of his cases. The specialist in dermatology should, whenever necessary, be glad to call upon a man with further intensive and special training in the particular direction of allergy and immunology as applied to cutaneous diseases. Unfortunately, few, if any, such allergists with particular training in dermatologic allergy are at present available. I believe that in dermatology, as well as in other specialties and in medicine in general, the fundamental biologic concepts of allergy will never come into their own until the role of the practicing allergist becomes a rational one—a consultant role analogous to that of the hematologist or radiologist or endocrinologist. For this purpose the specialist in allergy must receive adequate training, not in the entire field of diagnosis and treatment of skin diseases, but in those particular dermato-allergic aspects of medicine which will enable him best to fulfill his complementary function in the management of cutaneous diseases.

DR. KERN.—Allergy, an unknown term a few years ago, has become a by-word on the streets. That the public needs information about allergy is obvious, particularly from the standpoint of preventive medicine. That the public is getting much that is misinformation is equally obvious. What can and should we do about it? The symposium concludes with a discussion of

Allergy and the Lay Public. ALBERT VANDER VEER, M.D., New York, N. Y.

Those of us who work in allergy day in and day out are prone to make the mistake of thinking that everyone is as conversant with the subject as we are. This is far from the case, although the meaning of allergy, its symptoms, prevention, and treatment, is vastly better understood among the laity today than ten or fifteen years ago. With or without our help the discussion of this subject is certain to spread, and it is our duty to aid in the dissemination of accurate, helpful information, and to discourage fantastic and miraculous claims which are bound to arise in any new field. One of our first efforts should be to educate the public in the proper meaning of the terms vaccine,

serum, extract, and antitoxin, which are now used by them so glibly and apparently interchangeably. Many parents hesitate to have their child vaccinated for smallpox or given pertussis or typhoid vaccine because of the tales they have heard of the severe reaction which may follow a serum injection.

The most effective way to educate the laity is to work through the family physician. Therefore we should lose no opportunity to present the subject at medical meetings. The simpler cases due to feathers, pets, house dust, etc., should be recognized and treated without being brought to the specialist. Those who do not respond within a reasonable period of time should, of course, be given more intensive study. We should also constantly emphasize to the rhinologist that many of his patients are allergic and must have competent treatment before resorting to useless packs and local treatment, and before surgical removal of pathologic conditions. The pediatrician and the skin specialist are apparently more eager to make use of the rapidly increasing knowledge of allergy than either the general practitioner or the rhinologist.

In reaching the laity through the medical profession we must be conservative in our statements and stick to fundamentals which have stood the test of time. In our special societies it is legitimate to report new investigations and discoveries, but these should not be passed on to the laity until they have been substantiated. It is right and proper that articles dealing with the proved facts of allergy should appear in health journals, such as *Hygeia, The Parents' Magazine,* and *The Ladies' Home Journal.* These should be written in simple language, avoiding technicalities as far as possible, but they should deal little or not at all with subjects still controversial. The latter should be reserved for medical magazines where they will come under the scrutiny of men more qualified to pass judgment on their truth or error. Physicians are accustomed to view reports of miracle working in medicine with skepticism and to weigh the reputation of the discoverer, but the laity has no ability to separate the sheep from the goats. To them a doctor is a doctor and if he comes from far countries so much the more glory.

Radio talks on scientific subjects are becoming more and more popular and here too we can reach a large audience. The same care should be taken as with magazine articles and, if possible, all publications and radio addresses should first be submitted to an official censorship committee, such as the Academy of Medicine, County Medical Society, or special allergic societies. This gives an official stamp of approval, shares our responsibility, and occasionally may save both author and medical profession from an embarrassing situation.

In recent times emphasis is being placed more and more on the prevention of disease, and allergy furnishes a splendid field for this, as we are warned long ahead of time where to look for its appearance. This, of course, is due to the inheritance factor which has been fully proved. How carefully we watch the children of parents with a family history of tuberculosis, syphilis, diabetes, epilepsy, or cancer to ward off the danger of similar occurrence in the offspring, and yet I doubt if any of these diseases will show a higher rate of inheritance than allergy. Do not let yourselves be deceived with the argument that these other diseases are dangerous to life and crippling, while hay fever is a very minor ill and hardly worth bothering about. Follow the life history of a child who gets a bad start in the developmental

period of life due to a sensitiveness to milk, or suffers from severe asthma due to pets, dust or feathers until its chest is bent out of shape, and structural changes have taken place which can never be repaired. Get the personal history of a girl whose social life has been ruined by eczema, not dangerous to life, but as crippling to her happiness as infantile paralysis would be. We have all seen the chronic infective asthmatic of 40 or 50, unable to work steadily or at all, a burden to his family, and his life a constant agonizing struggle to get breath into his body. Certainly most of us would prefer a shorter decisive battle with tuberculosis or cancer, but with the chance of permanent cure.

Parents with allergic family histories should be taught that their children very possibly will be allergic. This must, of course, be done tactfully, and we can honestly say that the vast majority of allergic complaints are not serious and can be easily rectified if taken in time. We cannot, however, tell which particular patient is going to have a simple, easily treated hay fever and which is doomed to chronic sinus infection and asthma. Because many do escape serious damage is no excuse for putting our head in the sand and saying, "Don't worry, he will outgrow his trouble in time." Allergic parents should be taught that a constant succession of respiratory infections in their child may require more than the simple removal of tonsils and adenoids, and, while feather pillows and pets may be fine for the average child, they are rank poison for their own darling. Chronic indigestion and failure to gain weight may not be due to the richness of the milk but to the milk itself, or to the cod-liver oil tonic. Adults with hay fever or chronic sinus infection should be told that while the trouble is so mild at the present time it is hardly worth bothering about, it may not always remain so, and a well-developed chronic infective asthma is hard to get rid of.

The laity should be told that the time to treat an allergic condition is when it is discovered, not when it becomes serious. We do not knowingly allow tuberculosis to go on to cavity formation or observe cancer until the neighboring lymph glands are involved before recommending drastic measures. I know of no disease where an ounce of prevention is of more value than in allergy.

In every case where allergy is suspected the family physician should first be consulted. His knowledge of the family history and the patient's past history may prove invaluable, and if the case is not too complicated, he can usually outline a course of treatment that will prove successful. If the case is complicated or does not improve within a reasonable space of time, a specialist should be consulted.

To summarize: The best way to make the public allergy conscious is (1) through the general practitioner, the pediatrician, and the rhinologist; (2) by simple, sane articles in health magazines which have a wide circulation among the laity. In our educational work we should try to make our language simple and understandable. We should continually stress the fundamentals, although we may feel that we are only repeating what everyone must know by now. The vast majority of the public still knows little or nothing about allergy and much of what they think they know is wrong. We should continually emphasize the necessity of early diagnosis and treatment no matter how trivial the present manifestations may seem. By so doing much future trouble may be avoided.

Selected Abstracts

Asthma and Hay Fever

UNDER THE DIRECTION OF SAMUEL M. FEINBERG, M.D., CHICAGO

Epinephrine in Oil. A New, Slowly Absorbed Epinephrine Preparation. Keeney, E. L., Pierce, J. A., and Gay, L. N.: Arch. Int. Med. **63**: 119, 1939.

The authors investigated the prolongation of therapeutic effect of epinephrine suspended in oil. They used epinephrine base powder in peanut oil so that 1 c.c. contained 2 mg. of epinephrine. In 10 patients with chronic asthma receiving either frequent injections of epinephrine hydrochloride or inhalations of the same, injections of 0.65 to 2.0 c.c. doses of the epinephrine in oil mixture produced relief lasting from eight to sixteen hours. In 11 patients who received this suspension during one or more acute attacks of asthma, the duration of relief was from nine to sixteen hours. Encouraging results were also obtained in urticaria and serum sickness. The injections are usually given subcutaneously. Consecutive injections may become irritating, and the authors advise giving the material intramuscularly when that happens. The hyperglycemia and cardiovascular responses to this material are maintained for eight or nine hours, but are not as marked as with the aqueous solutions of epinephrine.

Use of Therapeutic Iodized Oil in Treatment of Bronchial Asthma. Moore, M. W.: Northwest Med. **38**: 55, 1939.

The results attained in the treatment of 35 cases of bronchial asthma with therapeutic iodized oil (a poppy-seed oil containing 22 to 25 per cent iodine, not in the free form) were not encouraging to the author. The cases were studied further to determine if there was some criterion by which one could select certain types which probably would obtain beneficial results with iodized oil. He found that those patients with bronchiectasis or productive cough were more apt to be benefited. He tabulates the indications as follows: (1) bronchiectasis, (2) history of excessive productive cough, (3) failure to respond to the usual forms of accepted therapy, and (4) otherwise a strong, healthy individual. The contraindications he mentions are more numerous than the indications and he lists them as follows: (1) active pulmonary tuberculosis, (2) reduced vital capacity of the lungs, (3) acute pulmonary infections, (4) foreign bodies, (5) during an acute attack of asthma, (6) cardiac weakness, (7) late bronchial malignancy, (8) sensitivity to iodine, (9) sensitivity to poppy seed, and (10) extremity of life. In the 35 patients reported, one developed acute iodine poisoning with recovery in a week, and another developed bronchopneumonia.

In spite of the fact that the indications may be considered and the contraindications carefully studied, the procedure still has some elements of danger.

Autogenous Streptococcus Vaccines in the Treatment of Allergic Conditions, With Special Reference to Their Use in Bronchial Asthma. Ylvisaker, R. S.: Minnesota Med. **22**: 6, 1939.

The author treated 14 cases of bronchial asthma (all but 2 were of the infectious type) and 9 miscellaneous cases, comprising 4 with allergic rhinitis, and one each of recurrent sinusitis, eczema, chronic urticaria, chronic conjunctivitis,

and chronic iritis. Treatment consisted of injections of autogenous vaccine, given intravenously in the majority of cases, and prepared from cultures made from the sputum, nasal mucosa, pharynx, tonsils, cervix uteri, rectal mucosa, or any other possible focus of infection. The organisms used were mostly of the streptococcus type. The patient was treated with those strains that gave a positive reaction of the immediate type to the undiluted filtrate intradermally.

Treatment was carried on for at least six months; injections were given at first every three to five days, and after improvement was established the interval was lengthened to five to seven days. The doses were extremely small and very gradually increased. Reactions called for a reduction in dosage. In the 14 bronchial asthma cases there were 3 failures; 4 had complete relief, 5 showed marked improvement, and 2 were moderately improved.

The author believes that the so-called infectious or bacterial type of allergy is fundamentally similar to other forms of allergy, and that the beneficial results obtained are due to specific desensitization and not to foreign protein shock. He states that the intravenous route of administration produces more prompt and precise results than the subcutaneous. He warns that severe reactions may follow if the dose is too large or if there is too long an interval between injections.

The Climatic Treatment of Hay Fever and Asthma With Special Reference to Florida. Metzger, F. C.: J. A. M. A. **112**: 29, 1939.

Metzger discusses the air-borne pollen in Florida. He finds that the amount is small, the variety limited, and the season practically all year. The concentration of ragweed pollen is small, and all persons sensitive to this allergen should be free from symptoms on the east coast near the beach. The mid-state section and the west coast are suited to all except those highly sensitive. Since 1925, ragweed has increased in the state due to more building and road construction. Slides exposed in Miami rarely showed any ragweed pollen, but a series of slides at Coral Gables, seven miles west, showed a count as high as 1,000 in 1935. Pollination in Tampa occurs about the middle of August, but at Ellenton, 35 miles south, it begins as early as May 10. By the middle of November the ragweeds are dead.

Grass pollen causes little trouble except to those highly sensitive. Bermuda grass is the most important pollinator, the season being all year with heaviest pollination in March and April, and a second peak in June and the first part of July. Of the trees the oak is the most important, pollinating as early as January 20 and continuing for six to eight weeks. In the northern section pecan pollen is a source of trouble. In February and March *Eucalyptus* tree pollen may be a source of pollinosis in towns and cities. Asthmatics whose sensitivity is predominantly dust are advised by Metzger not to go to Florida, since he believes that the local dust allergen is stronger than that found in northern sections. The chief foods found to be a primary or contributing factor in allergic rhinitis were citrous fruits, condiments, and sea foods. These foods, being abundant and inexpensive in Florida, are eaten in excess. The author believes that this observation supports the hypothesis that in individuals with a tendency to food allergy sensitization is more apt to occur to those foods eaten in excess.

Metzger is of the opinion that in selected cases where nonspecific causes and psychic factors are important, the climate of Florida may be beneficial. He advises that the physician should investigate the sensitivities of the patient and the distribution of the allergens in Florida before recommending a change of climate.

Atmospheric Pollen of Nashville, Tenn. Bowie, E.: J. Lab. & Clin. Med. **24**: 342, 1939.

The author describes the pollen content of the air of Nashville, Tenn., for 1936 and 1937. Ragweed begins pollinating about August 15 and is the most

important cause of fall hay fever. Other fall pollinators are annual wormwood *(Artemisia annua)* and varieties of chenopods, such as lamb's quarters *(Chenopodium album)*, Mexican tea *(C. ambrosioides)*, and Jerusalem oak *(C. botrys)*. Burning bush and pigweeds also pollinate in the fall. In September and in the first part of October an important pollinator is the fall-flowering elm *(Ulmus serotina)*.

Grass pollen is found in small quantities from spring until frost. The varieties encountered were those of blue grass, orchard, rye, Bermuda, Johnson, and others. The Bermuda and Johnson grasses may also pollinate during the fall.

In the spring one of the earliest pollinators is the elm, which accounts for most of the pollen in the air in March. Other important tree pollens are oak (in April and May), beech (April), hackberry (April), hickory and walnut (latter part of April and May), maclura (May) and mulberry (April and May).

Dermatology

UNDER THE DIRECTION OF JOSEPH GOODMAN, M.D., BOSTON

Increase in Allergic Reactivity by Hormones. Sylla, A.: Klin. Wchnschr. **18:** 311, 1939.

The author performed graded tuberculin tests on individuals who were given sex hormones by injection or by mouth. The purpose of the investigation was to discover whether there was any change in the reactivity of the skin to a specific allergen when reactions before and after the administration of the hormones were compared.

After three injections of 50,000 units of estrogenic substance (in the females) or 25 mg. of male sex hormone (in the males), given daily or every other day, there was a general increase in sensitivity to tuberculin. In some instances the sensitivity was one thousand times as great after administration of the hormone (a rise for instance, from a reaction to a dilution of 1:1,000 to a reaction from a dilution of 1:100,000). Thyroid and anterior pituitary preparations were found to have a similar effect.

An increase in sensitivity to tuberculin was noted after the administration of these hormones in practically all of the 30 patients with rheumatism and the 6 normal individuals on whom it was investigated.

Anamnestic Reaction of Tuberculin. Preliminary Report. Novak, J. B., and Kruglick, J. S.: Am. J. Dis. Child. **57:** 570, 1939.

The tests reported in this paper were performed in a manner designed to test the effect of a negative tuberculin test on a subsequent tuberculin test. Four hundred and seventy-three individuals were tested by the intracutaneous injection of one-tenth of the second strength of purified protein derivative. Of this group, 103 (22 per cent) reacted negatively. These individuals were retested immediately with the same amount of the original test material. There were 23 positive tests and 80 negative reactions.

The authors believe that in the patients who reacted first negatively and then positively, they demonstrated a reawakening of a dormant tuberculin allergy.

Diphtheria Scratch Test. Grozin, M.: Am. J. Dis. Child. **57:** 564, 1939.

The author compared on 100 children the results of the Schick test with the results of a scratch test with diphtheria toxin. In 92 instances there was agreement between the two tests. In one instance the Schick test was positive and the

scratch test negative, while in 4 instances the Schick test was negative and the scratch test positive. The other discrepancies (3 in number) involved questionable reactions to one or the other test.

The test is recommended on the grounds of simplicity of performance and sensitivity.

Cutaneous Hypersensitivity to the Procaine Anesthetics. Goodman, M. H.: J. Invest. Dermat. **2**: 53, 1939.

The patient studied presented a contact dermatitis from procaine and larocaine used in the eye. Extensive testing of this patient with aminobenzoate anesthetics and with various other local anesthetics revealed a specific hypersensitivity to the substituted aniline base, para-aminobenzoyl. All anesthetics built on this base as well as related nonanesthetics built on the same base, produced positive patch test reactions in the patient studied. Anesthetics of the cocaine, quinoline, and pyridine groups produced no reaction.

Photoallergy and Primary Photosensitivity to Sulfanilamide. Epstein, S.: J. Invest. Dermat. **2**: 43, 1939.

The intradermal injection of 0.1 c.c. of a 1 per cent solution of sulfanilamide followed by exposure to ultraviolet irradiation or to natural sunlight resulted in all instances in an erythematous reaction at the site of the injection, appearing one to twenty-four hours after the injection. On the tenth day an inflammatory, urticarial, pruritic eruption appeared spontaneously at the injected site, in 2 of the 6 individuals injected. Each subsequent injection into these two sensitized individuals resulted in a similar urticarial response which now appeared ten to twenty-four hours after the injection and exposure to ultraviolet light.

The photosensitivity thus produced in the 2 individuals who presented urticarial reactions met all the requirements of a true allergic hypersensitivity.

Karaya Gum as a Cause of Urticaria. Bowen, R.: Arch. Dermat. & Syph. **39**: 506, 1939.

Five instances of urticaria produced by the ingestion of Karaya gum are reported.

In one patient the dermatosis simulated a fixed drug eruption but was accompanied by a positive scratch test to an extract of Karaya gum. A list of substances which contain Karaya gum is given.

Immunology

UNDER THE DIRECTION OF MATTHEW WALZER, M.D., AND MAX HARTEN, M.D., BROOKLYN

Anaphylaxis in the Rhesus Monkey. I. Horse Serum as an Antigen. Kopeloff, L. M., and Kopeloff, N.: J. Immunol. **36**: 83, 1939.

The authors report their studies on anaphylaxis in the *Rhesus* monkey with horse serum as the antigen.

Twelve monkeys received repeated intravenous injections of normal horse serum at intervals of from two to eight weeks over an eight-month period. The initial injection of 20 c.c. of horse serum per kg. of body weight in 3 monkeys produced "collapse" in one and less severe reactions in the other 2. The other 9 monkeys received initial injections of 10 c.c. of horse serum per kg. Subsequent injections varied from 10 c.c. to 20 c.c. per kg.

Of 10 monkeys which had received 4 or more sensitizing injections, 6 were fatally shocked. Severe reactions including prostration were observed in the 4 survivors. Fatal shock occurred in from thirty minutes to twenty-four hours after administration of the shocking dose. Common symptoms during the reactions included increased respiratory rate, salivation, vomiting, prostration with or without loss of consciousness, gasping, and cyanosis. When fatal shock was delayed for twenty-four hours, edema of the face was noted. Bleeding from the anus was frequently observed. Mild shock consisted of weakness and vomiting.

In 2 of the 4 animals which survived, edema of the face associated with marked hemorrhage about the eyes and in the conjunctivae was noted. In one animal hemorrhagic areas appeared over the entire body within six hours after the shocking injection and persisted for forty-eight hours.

The degree of sensitivity, as measured by shock, and the precipitin titer did not appear to be correlated.

Subcutaneous and intracutaneous test doses of horse serum in sensitized monkeys produced specific positive skin reactions, characterized by hemorrhage, edema, and necrosis, which were interpreted as Arthus reactions.

The writers were unable to sensitize monkeys passively by the intravenous injection of a potent antihorse serum-rabbit serum. Guinea pigs were readily passively sensitized with antihorse serum-monkey serum.

The most striking pathologic changes, following fatal shock with horse serum in actively sensitized monkeys, were edema and hemorrhage of the skin, lungs, intestines, and other internal organs. A marked reduction in blood platelets and delay in clotting time followed the shocking dose of horse serum.

Cutaneous and intravenous testing demonstrated the specificity of the hypersensitiveness.

The Schultz-Dale test for hypersensitiveness proved negative with both uterine and intestinal muscle strips of the sensitive animals.

The authors conclude that, despite the apparent discrepancies between the above findings and those seen in classical anaphylaxis in other laboratory animals, the reaction described is anaphylactic in nature.

Anaphylaxis in the Rhesus Monkey. II. Egg White as an Antigen. Kopeloff, L. M., and Kopeloff, N.: J. Immunol. **36**: 101, 1939.

In previous investigations the authors reported that *Rhesus* monkeys could be sensitized and shocked with "liberal" amounts of undiluted hen's egg white. They deemed it advisable to investigate this question further, using smaller amounts of egg white.

Nine monkeys were given 3 intravenous injections of 1 c.c. per kg. of undiluted egg white on alternate days, and 4 animals received 6 sensitizing doses of 0.5 c.c. per kg. on alternate days. All animals were shocked intravenously from five to twenty days later with 1 c.c. of undiluted egg white per kg. Anaphylactic reactions of varying degree were obtained in 12 of the 13 monkeys tested. Multiple sensitizing injections thus proved more effective for sensitization than the single dose of antigen employed in previous experiments.

The symptomatology of severe shock included collapse within one minute, unconsciousness with temporary cessation of respiration, followed by infrequent gasping, occasional goose flesh, cyanosis, coarse tremors of the extremities, and finally death or gradual recovery. Mild reactions consisted of weakness, retching, and vomiting in varying degree.

The sensitivity to egg white in one series of animals was found to persist for from five to twelve months.

Precipitins to egg white could be demonstrated only after multiple sensitizing injections, but not after a single sensitizing dose. The titers were usually very low.

Specific positive skin reactions were obtained by intracutaneous or subcutaneous tests in actively or passively sensitized animals. Arthus reactions were also induced.

Successful passive transfer of sensitiveness was reported in 3 of 4 monkeys with anti-egg white rabbit serum. The removal of egg white precipitins from the serum by specific absorption rendered it ineffective. Passive sensitization was also induced with anticrystalline ovalbumin rabbit serum. Previous unsuccessful attempts to induce active sensitization in the monkey with crystalline ovalbumin are attributed to the inability of this animal to produce precipitins to this antigen. Successful passive transfer in monkeys with pooled anti-egg white monkey serum was also reported.

The Schultz-Dale test proved negative on uterine and intestinal strips excised from monkeys known to be highly sensitive to egg white.

The pathologic findings following acute fatal shock consisted of occasional emphysema of the lungs with petechial hemorrhages, or dilatation of the heart. Following shock, the blood platelets were reduced in number and the clotting time was delayed.

Dilution, or filtration of undiluted egg white through paper, diminished its capacity for sensitization, desensitization, and shock. No adequate explanation for this is offered.

Histology of the Cutaneous Reaction to Brucella Melitensis Antigen. Gersh, I., and Black, W. C.: Arch. Path. **27**: 307, 1939.

The absence of any report in the literature on the cutaneous reaction to *Brucella* antigen in man prompted the authors to undertake this study.

Intracutaneous tests were performed with 0.1 c.c. of *Brucella* antigen on the anterior forearm. Specimens from 12 patients were removed for histologic study; 4 at forty-eight hours, 2 at seventy-two hours, 2 at ninety-six hours, and 1 each at one hundred twenty, one hundred forty, one hundred sixty-eight, and one hundred ninety-two hours, respectively. The specimens were fixed in formaldehyde and stained by Gram's method and with pyronine-methyl green.

The general features of the reaction were inflammatory in nature, consisting of a cellular infiltrative process in which slight to moderate edema was present. Collections of cells in the loose areolar connective tissue of the corium around the blood vessels, nerves, hair follicles, sweat and sebaceous glands were noted. The epidermis and coarse collagenous fibers were altered only in severe reactions where necrosis occurred. Small foci of necrosis in the derma were present at forty-eight hours. Variation in the intensity of the reaction at the same time interval in different individuals was interpreted by the authors to indicate a probable difference in the degree of sensitivity. The infiltrating cells were predominantly lymphoid in character. No giant cell formation and no eosinophiles were observed.

On the whole the histologic picture resembled the reaction to tuberculin as described by Dienes and Mallory. It differed from the tuberculin reaction in that necrosis began in the corium rather than in the epidermis.

On the Resistance of the White Rat to Shock. St. Went and Martin, J.: Arch. f. exper. Path. u. Pharmakol. **191**: 545, 1939.

The authors review the pertinent available literature on the resistance of the white rat to anaphylactic shock and report their own investigations on this subject.

White rats, weighing 150 to 200 gm., kept on a mixed diet of milk, bread, and vegetables, received an intraperitoneal injection of 0.5 c.c. of bovine serum followed by a second injection of 0.3 c.c. after three days.

The animals were shocked from twenty-one to thirty-five days later by the intravenous injection of 0.5 c.c. of homologous antigen. Using a special perfusion apparatus, the writers investigated the contraction of the bronchial musculature and functional changes occurring in the isolated heart of sensitized rats.

The re-injection of from 0.2 c.c. to 0.8 c.c. of bovine serum produced no effect on the blood pressure in sensitized rats. The injection of 0.5 mg. of histamine resulted in a marked lowering of blood pressure. No bronchospasm was observed in the perfused lungs of sensitized animals after 1 c.c. of a 1:100 dilution of the antigen was injected into the perfusate. One per cent acetylcholine, used as a control, produced a definite bronchospasm which was relieved by adrenalin.

In the isolated heart of sensitized guinea pigs the authors had previously reported the occurrence of functional changes during anaphylaxis. No such changes were observed in the sensitized white rat. One per cent histamine produced marked ionotropic and chronotropic effects in the isolated heart of sensitized rats.

Rats have proved resistant to many other substances. Acetylcholine must be used in 1:100,000 dilution to produce a reaction in rats, whereas in guinea pigs a reaction can be obtained with a dilution of 1:20,000 million.

The authors conclude that at least three factors are responsible for the resistance of rats to anaphylactic shock: (1) the ability of the smooth muscle elements to prevent the entrance of substances into the cells (Coca); (2) reduced sensitivity of the autonomic nerve endings; and (3) compensatory function of the adrenals.

The Immunological Properties of Proteins Treated With BB′ Dichlorodiethyl Sulphide (Mustard Gas) and BB′ Dichlorodiethyl Sulphone. Berenblum, I., and Wormall, A.: Biochem. J. **33**: 75, 1939.

Immunologic investigations have been reported to support the theory that the vesicant action of mustard gas and related compounds might be due to a reaction between the mustard gas and the amino acids present in the skin. The present studies were undertaken to determine whether immunologic methods would enable the detection of a reaction between mustard gas and proteins and to study the general immunologic properties of mustard gas-treated proteins.

Normal horse serum was treated at room temperature with mustard gas (BB′ dichlorodiethyl sulfide) and "sulphone" (BB′ dichlorodiethyl sulphone). Rabbits, sensitized by 3 to 7 intraperitoneal injections of mustard gas-treated horse serum and sulphone-treated horse serum produced precipitin antibodies specific for the injected antigens (a new specificity having been acquired by the horse serum antigen). No cross reaction between sulphone-treated horse serum and mustard gas-treated proteins was observed.

The authors note that a possible chemical basis for this change in immunologic properties may be an interaction between the mustard gas (or sulphone) and the free amino groups of the protein molecule.

A Study of Antigens and Antibodies by the Monolayer Film Technique of Langmuir. Shaffer, M. F., and Dingle, J. H.: Proc. Soc. Exper. Biol. & Med. **38**: 528, 1938.

Langmuir, by adsorbing dissolved substances onto the surface of suitable plates covered with multiple monomolecular layers of stearate, was able to study various properties of adsorbed films and determine the thickness of monolayers of egg

albumen, diphtheria toxin, etc. The authors, in the present investigation, report their studies of several antigen-antibody systems with the aid of the Langmuir technique.

Y-films of stearate were prepared by depositing the desired number of layers on polished chromium surfaces. A small amount of the solution under investigation was applied to the stearate surface and rubbed over it to assure adequate exposure. The film was then washed, dried, and the change in thickness due to the adsorbed layer measured by the use of simple optical techniques.

A 2 per cent aqueous solution of crystalline egg albumen applied to the surface of stearate wetted it readily. The area of albumin-treated stearate showed an increase in thickness of approximately 40 Å. Antiovalbumin rabbit serum applied to the albumin-treated surface further increased the thickness by 100 Å. An attempt was made to deposit a second layer of egg albumen onto the upper surface of the specific antibody, already adherent to a first layer of albumin. This procedure resulted in a removal of the antibody, and left attached to the stearate surface only the original albumin layer. The specificity of the reactions, when immune sera were applied to antigen-treated areas, was shown by the fact that the antisera did not adhere when applied directly to a stearate surface, although they wetted it. Normal rabbit or horse sera, or heterologous immune sera of horse or rabbit, failed to adhere to a stearate surface on which a monolayer of antigen had been deposited.

Studies with types V and VIII antipneumococcus sera suggest that in the horse at least the size of the antibody protein molecule or aggregate varies according to the type of pneumococcus employed in its production.

The authors conclude that the monolayer film method provides a valuable means for the study of antigen-antibody systems as regards molecular dimensions, combining properties, and other aspects of their behavior.

Pediatrics

UNDER THE DIRECTION OF WILLIAM C. DEAMER, M.D., SAN FRANCISCO

Allergy in Infants. Significance of First Allergic Manifestations. Clein, N. W.: Northwest Med. **38**: 9, 1939.

A series of 100 allergic and 100 nonallergic infants were studied from birth to 5 years of age under more or less uniform conditions. In the allergic group 71 per cent had allergic parents, whereas 12 per cent of the control group had allergic parents. In the allergic group 78 per cent exhibited their allergic symptoms before 4 months of age. The symptoms complained of were rash (eczema), 85 cases, occurring chiefly on the face; excessive vomiting (pylorospasm), 24 cases; colic (abdominal pain, gas, or diarrhea), 16 cases.

The author believes sensitization can occur through breast milk. He cites 9 out of 12 cases on breast milk alone in which allergic symptoms were relieved by changes in the mother's diet. He does not discuss the possibility of intrauterine sensitization. He believes most cases of pyloric stenosis are probably chronic allergic pylorospasm and cites recent lowering of the per cent requiring operation as support of this belief.

About half of the allergic group received egg yolk before four months of age, and 90 per cent of those who received it showed allergic symptoms as a result. The symptoms shown were chiefly rash or vomiting, but also included constipation, pain, gas, diarrhea, and refusal of food.

Geographic tongue is stated to be pathognomonic of the allergic state, and carotinemia to occur practically always in allergic babies. Skin tests are not discussed, but the author indicates that he considers inhalants of importance as well as foods.

Transient Lung Consolidation in Asthmatic Children With Reference to Eosinophilia. Söderling, B.: Arch. Dis. Childhood **14**: 22, 1939.

The author points out that what has been described on the continent as Loeffler's syndrome (transient pulmonary infiltrations with blood eosinophilia) and what Egel of Shanghai has called "edema *allergicum pulmonis*" in patients with seasonal "privet cough," and several cases of transient lung consolidation in asthmatic children reported by him are probably all instances of the same clinical syndrome. Loeffler emphasized the transient and wandering nature of the pulmonary infiltration, the comparative absence of clinical signs and symptoms, and the eosinophilia which could reach as high as 66 per cent and which spoke for an "anaphylactoid" process. Egel described an interesting summer cough in a large percentage of the inhabitants of China which was commonly referred to as privet cough, privet being a species of *Ligustrum* flowering at the time. A certain number of patients also showed transient pulmonary consolidations and a blood eosinophilia, although not particularly ill.

Söderling feels that the transience of the consolidation should be stressed more than the eosinophilia of the blood. The latter may even be absent. Furthermore, the occurrence of the complaint in asthmatic persons should be emphasized as also the possibility of a simultaneous infection which may change the blood picture, the otherwise normal sedimentation rate and the general condition of the patient. He feels that x-ray examination is essential to diagnosis.

Transient Pulmonary Infiltration With Blood Eosinophilia (Loeffler's Syndrome). Weber, F. Parkes: Brit. J. Child. Dis. **36**: 15, 1939.

This is another report dealing with a case in a boy 10 years of age in which there occurred opacity of the lung in the x-ray film, eosinophilia, and absence of the usual signs of infection. The patient gave a history suggesting a chronic vasomotor rhinitis, and he had dermographism. The possible relationship to similar cases described as pneumonitis by Dr. A. M. Gill, in the *British Medical Journal*, which neither showed eosinophilia nor gave a history of allergy, is discussed.

The Treatment of Infectional Asthma in Children With Filtrates of Cultures of Upper Respiratory Pathogenic Bacteria. Stevens, F. A.: J. Pediat. **14**: 307, 1939.

Feeling that children offer the best conditions for studying the effects of immunization with bacterial filtrates, Stevens selected 53 instances which he felt represented infectional asthma. In the majority asthma occurred only in the winter after "colds." Onset had usually followed pertussis, pneumonia, a severe upper respiratory infection, or a series of colds of increasing severity. Intracutaneous tests with the common inhalants and important foods were all negative, and during the course of treatment sensitivities in these two groups did not come to light. Twenty-one had had previous unsatisfactory treatment for one or two years.

The treatments were given twice a week for several months, then weekly until the following summer. From 0.1 c.c. of a 1:100 dilution to 1.0 c.c. of the original filtrate was used. The filtrates were from mixtures of autogenous and stock cultures and represented all the pathogens ordinarily found by nose and throat cultures. Skin tests were not thought to have any significance etiologically or as a guide in treatment. In 34 children an attack of asthma occurred within twelve hours of an injection at some time in their series of treatments. In 3 an almost

continuous asthmatic state was induced by repeated overdosage. Treatment extended over a period of two years in most instances; in 15 it was carried out for three years.

Fifty of the 53 were relieved of their asthma by this type of treatment. Filtrates rather than vaccines were used because they had been effective in desensitizing patients with chronic infectional edema, while vaccines had not. The method has not been as successful in adults as it has been in children.

Problems of So-called Infantile Eczema. I. True Eczema. Tachau, Paul: Acta dermat. venereol. **19**: 587, 1938; **II. Atopic Dermatitis.** Acta dermat. venereol. **20**: 42, 1939.

Tachau differentiates atopic dermatitis and true eczema along the lines of Hill and Sulzberger. He attempts to correlate the varied and confusing terminology of the American and European literature in this field. In comparison with his previous experience in Braunschweig, Germany, he finds considerably more atopic dermatitis in infancy in Chicago and believes the frequency of atopic dermatitis and its relationship to asthma and hay fever subject to considerable geographic differences, probably dependent upon variations in exposures to potent allergens.

Concerning Bronchial Asthma in the Child. Cirlea, J., and Bogdan, L.: Arch. f. Kinderh. **116**: 65, 1939.

Two cases diagnosed as infantile asthma in infants of 7 weeks and 3 weeks are reported. In one a positive skin test to mother's milk and wheat was obtained; in the other, tests were negative. Both responded to adrenalin and had an eosinophilia of the blood.

Local Inhibition of the Tuberculin Reaction by Intracutaneous Injection of Eczema-Serum and Its Interpretation. Hilber, H.: Ztschr. f. Kinderh. **60**: 522, 1939.

Forty tuberculin positive children were injected intracutaneously with serum from egg-sensitive eczematous children. In 11 the tuberculin reaction was completely inhibited when it was put on twenty-four hours later; in 16 it was partially interfered with, and in the remaining 13 it was unaffected. There was no relationship with the tuberculous status of the recipient, whether active or not, and the outcome of the test. Controls with normal serum did not show the inhibiting phenomenon. The inhibiting effect was lost if the Prausnitz-Küstner reaction was completed by injecting an egg white solution (0.1 c.c. of a 50 per cent solution) before putting on the tuberculin test. Hilber interprets the observations as being due to a blocking of a second allergic reaction by egg antibodies previously fixed to the tissue cells. Variations in response are attributed to constitutional variations in antibody-fixing capacity of the skin cells. Some children completely lacking in this capacity were encountered.

Rhinology and Ophthalmology

UNDER THE DIRECTION OF FRENCH K. HANSEL, M.D., ST. LOUIS

Conservative Management of the Sinuses. Jervey, J. W., Jr.: South. M. J. **32**: 278, 1939.

In a discussion of the conservative management of the sinuses, Jersey considers in brief the most important phases of this problem. His statistics on the incidence

of sinusitis and allergy are interesting. During the years 1924 to 1928, 421 cases of sinusitis and 11 cases of allergy were noted among 1,566 ear, nose, and throat patients. From 1929 to 1933 there were 328 cases of sinusitis and 20 cases of allergy among 1,395 patients. From 1934 to 1938 there were 305 cases of sinusitis and 76 cases of allergy among 2,419 patients. Jervey stated that the diagnosis of sinusitis is gradually falling. Allergy and other conditions (nutritional disturbances and traumatic rhinitis) are increasing. It is noteworthy that the percentage of allergic cases increased from 0.7 per cent during the first five-year period to 3.1 per cent during the last five-year period. According to our statistics, the incidence of allergy among ear, nose, and throat cases is about 16 per cent, while among all nose and sinus cases it is about 40 per cent. The incidence of allergy in any individual private practice is proportional to the accuracy of the diagnosis of allergy.

Central Society for Clinical Research. Prickman, L. E.: (Discussion) J. A. M. A. **112**: 1102, 1939.

Of 26 carefully selected and studied cases of vasomotor rhinitis, Prickman noted definite relief from the use of histaminase in 9; or 34 per cent. In 4 instances the results were questionable; in the remaining 13 no relief whatsoever occurred. In patients who obtained relief the administration of the drug had to be continued, as it did not appear to produce desensitization.

Association of Stammering and the Allergic Diathesis. Kennedy, A. M., and Williams, D. A.: Brit. M. J. **2**: 1306, 1938.

In a series of 100 consecutive cases of stammering in children, Kennedy and Williams noted a positive family history of stammering in 65. Fifty-two children gave a personal history of allergic manifestations, and of these, 48 had a positive family history of stammering. It was concluded from these studies that the close and practically constant association of stammering and allergic manifestations in the personal and family histories of the stammerer rather favors the view that there is something more than a mere casual relationship between stammering and the allergic diathesis.

Procaine Idiosyncrasy and Cervical Phlegmon as Complications Following Local Anaesthesia for Tonsillectomy. Case Report. Harlowe, J. D.: Laryngoscope **49**: 123, 1939.

Harlowe reports a case of procaine idiosyncrasy in which following the injection of 0.5 per cent solution the patient complained of faintness, severe headache, dyspnea, and nausea. The patient became cyanotic, vomited, and developed a rapid and weak pulse, and then general clonic spasms began. The operation was not performed, but nine days later another physician injected a 1 per cent solution of procaine with epinephrine and the patient died on the operating table.

Dermatitis Due to Butyn. Parkhurst, H. J., and Lukens, J. A.: J. A. M. A. **112**: 837, 1939.

Upon a careful search of the literature, Parkhurst and Lukens could find reports of only 3 cases of dermatitis caused by butyn. They add a fourth case of a patient, aged 49 years, on whom 2 per cent butyn was used in the eye as a local anesthetic. The next day the patient had a marked swelling and itching of both eyelids on the right side. The following day there was a more severe dermatitis of the lids, with vesiculation and edema; the eye was swollen shut. An erythematous

vesicular streak, about 5 mm. wide, extended down the cheek to the chin, apparently following the path along which the solution had run. A positive patch test was noted twenty-four hours after application of the butyn to the skin of the arm. The opinion was expressed that such instances of sensitivity to butyn occur more frequently than the paucity of reports would seem to indicate. A case of sensitivity to butyn of a similar nature came under our observation only recently. The skin of the eyelids in both sides were markedly involved with a dermatitis. Eye drops containing butyn had been used. A positive patch test was demonstrated.

Miscellaneous

Atherosclerosis, Angina and Allergy. Werley, G.: Southwestern Med. **22:** 431, 1938.

Werley presents the hypothesis that allergy may be a causative factor in the production of coronary disease. He thinks that two effects are possible. One method may be that allergic reactions may damage the endothelial lining, favoring cholesterol infiltration into the intima and subsequent atherosclerosis. He believes that narrowing of the coronary arteries, or even complete closure, may not be sufficient to cause anginal attacks. He visualizes a sensitization of the coronaries and a consequent spasm due to allergy as the basis for the angina. The heavy smooth muscle coat in the coronary arteries suggests them as a favorable site for allergic reactions.

Anterior Pituitary Extract in the Treatment of Allergy. Bucher, C. S.: Clin. Med. & Surg. **45:** 160, 1938.

The author postulates that in allergy there is a deficiency in adrenalin production, and since anterior pituitary extract exerts a stimulating effect on the adrenals, the administration of such an extract might be beneficial. Several patients are reported who received such treatment, with very satisfactory results. It is maintained that such relief may be secured in 85 per cent of patients that are truly allergic.

Sodium Thiosulphate in the Treatment of Allergy. Klem, J. A.: Arch. Pediat. **55:** 197, 1938.

Based on the theory of Lumiere that anaphylaxis is due to alteration of tissue and fluid colloids in that they agglutinate and precipitate at the sites of allergic lesions, the author used sodium thiosulphate in the hope of changing colloid dispersion in such conditions. The drug was used both by mouth and intravenously in migraine, serum sickness, urticaria, and other allergic manifestations with very good results.

Note on Rapid Desensitization in a Case of Hypersensitiveness to Insulin. Corcoran, A. C.: Am. J. M. Sc. **196:** 359, 1938.

A patient of 56 with diabetes and cellulitis was given insulin for a period of time and it then was discontinued. It became necessary to use insulin again seven years later. This time an urticarial wheal always appeared at the site of administration, and after the eleventh injection the urticaria spread over the whole body. A history of hay fever in earlier years was then obtained.

Intracutaneous tests were made with 0.1 c.c. of beef, hog, sheep, and crystalline insulin. All reacted positively. Insulin was discontinued, but when its resumption

became essential a year later, hypersensitiveness was found to persist, and the value of rapid desensitization was tested by giving a series of injections of commercial insulin. The drug was administered intracutaneously at 7:30 A.M., when 0.2 unit was followed by a wheal of 4 sq. cm. The following injections of 0.2, 0.4, and 0.8 units were similarly given at 7:50, 8:10, 8:15, and 8:30 A.M. Injections were then given subcutaneously at intervals varying from fifteen to thirty minutes, and by 9 P.M. 32 injections had been given, the last 30 units intravenously without reaction. One hour later 4 units given intradermally produced but a slight wheal.

Action of Epinephrine and of Ephedrine on Anaphylactic Reactivity. Haag, F. E., Koenig, H., Kaun, H., and Wolters, G.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **91**: 22, 1937.

Guinea pigs sensitized with extracts of peas and treated repeatedly with epinephrine showed more severe anaphylactic reactions than the controls that did not receive epinephrine. It is concluded that epinephrine increases the anaphylactic reactivity of animals and that after prolonged administration it similarly raises the degree of hypersensitiveness in man. Aqueous and alcoholic extracts of *Ephedra vulgarus* decreased slightly the anaphylactic reactivity of guinea pigs that were already sensitized to extracts of peas. After extended administration the inhibitory action vanished. Repeated injections of the drug itself failed to sensitize the guinea pigs. Administration of ephedrine shortly or immediately before the shocking injection of protein did not affect the anaphylactic shock.

Thrombopenic Purpura Due to Food Allergy. Dutton, L. O.: J. A. M. A. **111**: 1920, 1938.

A case of thrombocytopenic purpura, allergic in origin, is added to those of Squier and Madison reported in 1937. The patient had periodic episodes of purpura with free intervals. The first attack followed the ingestion of a large quantity of citrus fruits. The purpura was associated with low platelets (60,000), moderate anemia, and relative leucopenia. The clot from drawn blood did not retract. Intracutaneous skin tests to orange, lemon, and several other foods were positive. A diagnosis of thrombocytopenic purpura due to citrus fruits was confirmed when the foods giving positive reactions were withheld and the lesions cleared. They reappeared when citrus fruits were added to the diet and cleared again on their removal.

Correspondence

The Editor, JOURNAL OF ALLERGY.

Dear Sir:

The members of the Chicago Society of Allergy, partly from their own experience, and partly from a survey of both the published and some of the unpublished experimental and clinical results of oral pollen therapy, believe that the evidence of beneficial effect is at present not sufficient to warrant the commercial promotion of material for oral pollen therapy. Because of their controversial and contradictory nature, the published results of oral pollen therapy are inadequate to justify the commercial promotion of such a product. In addition, our investigation indicates that many men who have used oral pollen therapy have failed to publish their work because of the unsatisfactory results obtained.

We, therefore, urge that the commercial promotion of oral pollen therapy should be deferred in the interest of the public and of the general practitioner until further experimentation now in progress has been reported.

B. Z. RAPPAPORT, President.

Montreal, Quebec,
March 10, 1939.

To the Editor, JOURNAL OF ALLERGY.

I wish to comment on the recent paper of Cohen in the JOURNAL OF ALLERGY, November, 1938, and on the summary on the relationship of vitamin C to hypersensitiveness, by Walzer, in the same number.

I was greatly interested in Cohen's study, and there seems to be no doubt that he has determined the degree of vitamin deficiency in his experimental animals with accuracy. In reading over the report, however, I was struck with the reactions noted in the protocols, and I must say that I would have been inclined to draw somewhat different conclusions than did Cohen.

In the first place, it must be noted that of the entire series of 110 guinea pigs, he lists but 25 as being sensitive to neoarsphenamine. However, of the pigs receiving less than 5 mg. of vitamin C per day, 14 of 27 showed suggestive evidence of sensitivity. This is a relatively small percentage of positive reactions, much smaller than would be expected in a controlled group of pigs. For example, using a vitamin C deficient diet, or the average winter fodder, which is low in vitamin C, I have been able to sensitize at least 75 per cent of all pigs with regularity. This low percentage suggests that some other factor, in addition to vitamin C, is operating to inhibit the development of sensitivity. This being the case, one cannot determine with definiteness the effect of vitamin C, however carefully the degree of deficiency is controlled. I found, in preliminary investigations, that different lots and brands of neoarsphenamine had different sensitizing qualities, and I was very much interested in the statement that the lot of neoarsphenamine used by Cohen was the same as that with which Sulzberger and Oser were able to produce sensitivity, with comparable regularity. I note that the guinea pigs used were of relatively large size, averaging from 600 to 1,000 gm. In previous experiments, by myself and by other authors, the guinea pigs used have been much smaller, averaging from 300 to 400 gm. On further studying the protocols, I obtained entirely different figures than did Cohen. Of the group of frankly scorbutic pigs, 4 out of 11 developed delayed reactions to the first injection of neoarsphenamine. Cohen lists but one reaction to the second injection, but this was largely determined on a one- to two-day study. I have previously noted that not infrequently when the diet was grossly deficient in vitamin C, the sensitized pigs did not react to the second injection until the third day. Sulzberger studied this same phenomenon and concluded that, in some instances at least, the failure to react to the second injection was due to cachectic anergy

(exhaustion of local tissue antibodies). With regard to the pigs which received 0.5 mg. of cevitamic acid, I find 10 pigs which showed suggestive reactivity; of those pigs receiving 5 mg., but 3 reacted, and of those receiving 10 mg., there were but 5 reactions. The protocols show further surprising reactions. There were 5 pigs, for example, which had strongly positive immediate reactions, and 7 others which showed 1-plus reactions to the first injection of neoarsphenamine. I have never seen this reaction in work including over 400 guinea pigs. As far as I know, guinea pigs are not inherently sensitive to the arsphenamines. There were several other instances in which there was a positive delayed reaction to the first injection of neoarsphenamine. This indicates, of course, a developing sensitivity and this in situ reactivity is evidence of allergic response in many related forms of developing hypersensitiveness. It is, furthermore, a little difficult to understand why, in several instances, there developed a delayed reactiveness to the second injection and not to the first. This was noted in pigs on both low and high vitamin C diets, and could not, therefore, be attributed to a deficiency of the vitamin. In any event, when it does occur, it suggests that sensitivity to neoarsphenamine is developing.

In summary, it seems to me that Cohen's paper confirms the previous work of Sulzberger and Oser, and of myself. The occurrence of false positive, immediate reactions to the first injection, however, raises a question of the dependability of the subsequent positive reactions. I was also interested in the experiment on the relationship of vitamin C depletion and an overdose of cevitamic acid to anaphylaxis. It would seem that vitamin C does not play a significant role in the development of anaphylactic states. It would be of value to confirm this impression in a series of experiments comparable to those recently reported by Landsteiner and Jacobs and by Frei and Sulzberger. These authors found that with old arsphenamine, not only could the skin of the guinea pig be sensitized, but anaphylaxis could be induced as well, if guinea pig serum, plus arsphenamine, were injected intravenously in previously sensitized pigs. This anaphylactic reactiveness, however, may not be directly associated with the reactions of the skin, and the only connective link seems to be that compounds which easily form conjugate proteins, have high skin sensitizing indices, in both animals and human beings. With reference to sensitivity to the arsphenamines in particular, the same probably holds true. When the arsphenamine is injected into the skin of the animal, oxidation, local tissue irritation, breakdown to arsene oxide and to other products, take place. The nature of the resultant conjugated protein has not yet been discovered. It apparently is not a conjugate with arsene oxide, since I have found that this compound (mapharsen) has a relatively low sensitizing index in guinea pigs, and that no anaphy-

laxis is produced when mapharsen, plus homologous serum, is injected intravenously in previously sensitized pigs. It may be that vitamin C, in its capacity as a reducing agent, in some way prevents the rapid oxidation of the arsphenamine, so that the tissue conjugates are not properly formed. I believe, nevertheless, that there is a definite action by vitamin C on the development of cutaneous arsphenamine reactiveness in the guinea pig.

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(Dr. Cormia's letter was submitted to Dr. Cohen.—*Editor.*)

Cleveland, Ohio,
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The Editor, JOURNAL OF ALLERGY.

When I repeated Sulzberger and Oser's experiments in 1935, using the same neoarsphenamine (sent to me by Sulzberger) and vitamin C from the same source, I did not obtain the per cent of sensitivity in my animals which had been reported by him or as described by Cormia in his published experiments and in his comments. Consideration of the experiment when it was finished made it obvious that no conclusions could be drawn with respect to vitamin C, since it was necessary to have better control of the dosage and of the diet.

It was with these ideas in mind that the second series of experiments were performed. I feel that the conclusions drawn are the only ones justified statistically from the protocols published. I hope that other workers will study the relationship of vitamin C to sensitivity further, using the basic principles outlined there, and feel that rather than to enter into any further discussions now, it will be appropriate to leave the matter to science and to time.

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